METABOLISM OF PESTICIDES

AN UPDATE

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By

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INTRODUCTION

In 1969 when METABOLISM OF PESTICIDES (Menzie 1969) was pub-
lished, it was still possible to condense the information into
one volume. The continued growth of interest in the subject
and the attendant volume of literature precluded such a con-
densation for the present volume. Consequently, this volume
was prepared as an update and supplement. Readers are advised
that a considerable body of literature may have been published
during the time required to prepare and print the present
volume.

ACKNOWLEDGMENTS

I extend my appreciation to all of those who took time to read portions of this manuscript and offered helpful comments. Thanks are particularly due Walter Benson, FDA; G. D. Paulson, USDA; Joseph Cummings, EPA; Gunter Zweig, EPA; and Charles Walker, FWS.

The _sine qua non_ of any manuscript is secretarial assistance. For this I am indebted to Maureen Matthews, Juanita Harvey, Dotty Coyle, and Judy Lundberg.

Finally, I thank a patient and understanding wife.

The fungus Paecilomyces sp. metabolized A-820 by loss of the alkyl group and by oxidation of the sec-butyl group. The latter could be an intermediate in the formation of 2,6-dinitro-4-tert-butylaniline (Kearney et al., 1972).

Normal laboratory illumination of the fungicide A-820 after application to a silia gel coated glass plate, for two months, effected little change. After seven hours of irradiation of a methanolic solution of A-820 with a borosilicate glass filter, there was little detectable change;
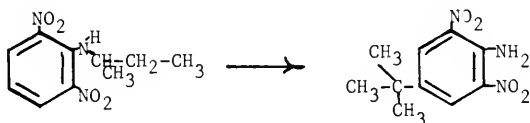
but irradiation through a corex glass filter produced at least 8 products after 4.5 hours. A saturated aqueous solution degraded slowly during illumination with a GE sunlamp. After seven days, there were two major products. The principal one was identified as 4-tert-butyl-2,6-dinitroaniline. The second was not identified (Plimmer and Klingebiel, 1972).

ABATE   [Bis-p-(O,O-dimethyl O-phenylphosphorothioate)sulfide]

Larvae of the mosquito (Aedes aegypti L.) metabolized Abate to sulfoxides and sulfones of Abate, the oxygen analog and the demethylated analog. Some conjugates were also formed.

In the housefly, all expected metabolic products were found internally either as the intact ester or as hydrolyzed material (Leesch and Fukuto, 1972).
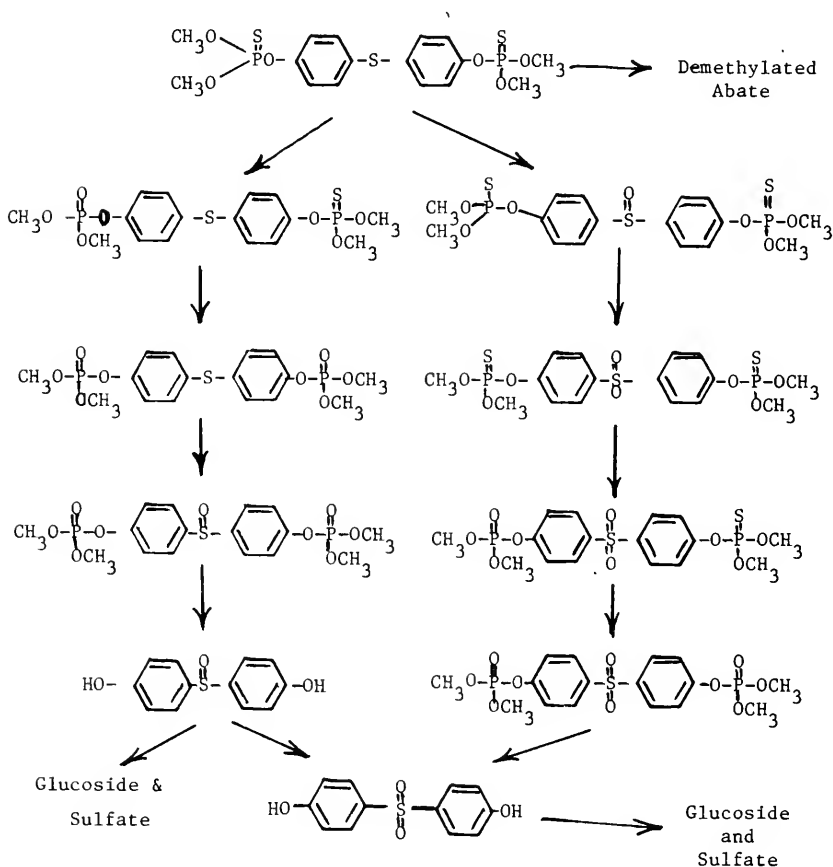
<u>ACCOTHION</u> (Fenitrothion, Sumithion) [$\underline{O},\underline{O}$-Dimethyl $\underline{O}$-(4-nitro-$\underline{m}$-tolyl) phosphorothioate]

When lactating cows were fed diets containing accothion, only the amino analog was observed in milk, urine, and feces (Johnson and Bowman, 1972).

The bimolecular rate constant for the inhibition of bovine erythrocyte cholinesterase by the oxon metabolite was determined at $37^{\circ}C$ to be $4.02 \times 10^4 M^{-1}min^{-1}$ (Braid and Nix, 1969).

Silage was prepared from fenitrothion treated corn and fed to lactating Jersey cattle for 8 weeks. In the silage were residues of fenitrothion, the oxygen analog, and its cresol. The amino analog of fenitrothion was found in milk of cows fed silage from fields treated at the rate of 3 lbs fenitrothion per acre but not when fed silage from fields treated at lower rates. The urine of the cows contained residues consisting mostly of the amino analog. Small amounts of the parent compound and its cresol were also present. Feces also contained primarily the amino analog (Leuck et al., 1971).

After treatment of Coastal bermudagrass and corn with accothion, analyses were conducted for residues. The parent compound disappeared rapidly. Residues of the oxygen analog were low and none were detected 21 days posttreatment. Residues of the nitrocresol were highest from one to seven days posttreatment (Leuck and Bowman, 1969).

In a forest environment, about half the initial accothion deposit was lost by foliage within 4 days and 70-85% within about 2 weeks after spraying. Loss from spruce was at a faster rate than from fir. The remainder was more stable than anticipated. Only traces of the oxon and nitrocresol were found at any stage (Yule and Duffy, 1971).

After the beetle <u>Tribolium castaneum</u> was topically treated with fenitrothion, the main hydrolytic metabolite was the O-demethyl analog. Dimethyl thiophosphate and dimethyl phosphate were also found. Fenitroxon and some phenol were observed (Dyte and Rowlands, 1970). Application of formic, acetic or n-propionic acid to <u>Tribolium castaneum</u> inhibited the formation of the oxon and desmethyl analogs. Attack on the P-O-Phenyl link, however, was not affected (Rowlands and Dyte, 1972).

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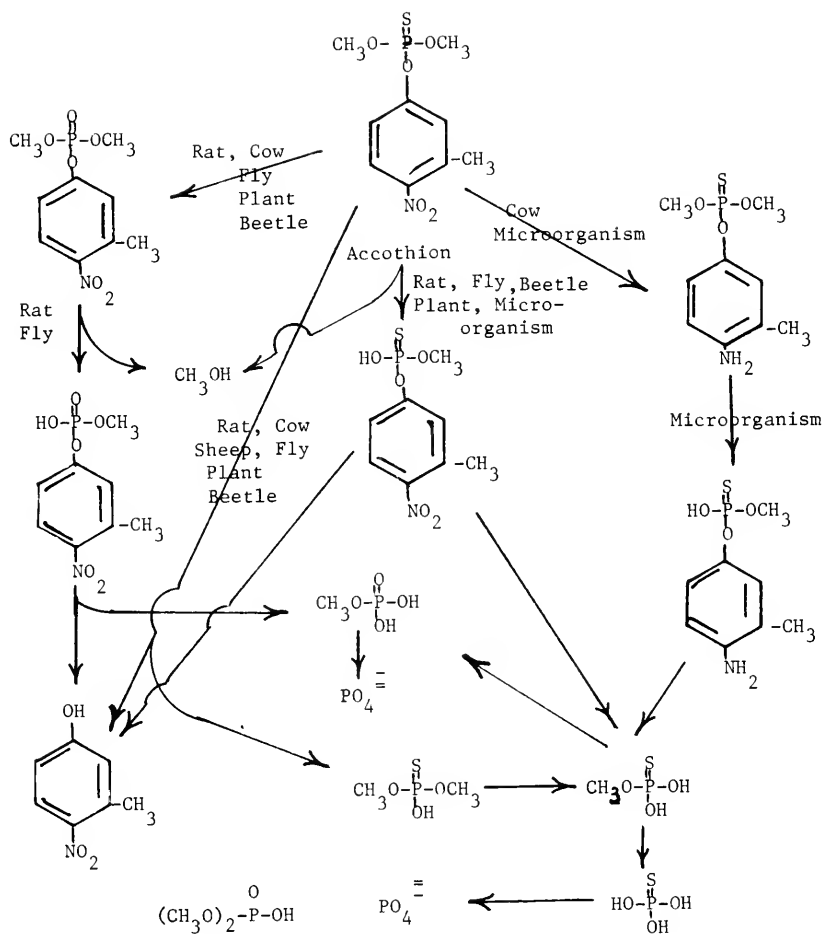
<u>ALACHLOR</u> [2-Chloro-2',6'-diethyl-<u>N</u>-(methoxymethyl)acetanilide]

Alachlor was applied to Sawyer fine sandy loam soil. At 22°C, relative humidity in a closed system had little effect on retention until humidity approached 100%. When the soil temperature was raised to 38°C or higher, relative humidity had a pronounced effect. Alachlor degraded to 2-chloro-2',6'-diethylacetanilide (Hargrove and Merkle, 1971).
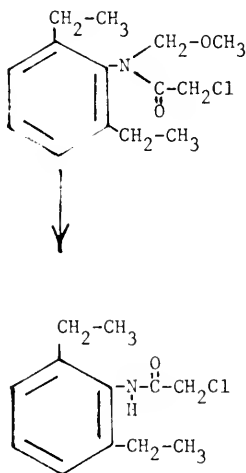
ALDICARB (Temik) [2-Methyl-2-methylthiopropionaldehyde O-methyl-
                    carbamoyl oxime]

Aldicarb(I) was fed to lactating cows for 14 days. In the milk,
about five unidentified compounds were observed in addition to
the sulfoxide and sulfones of aldicarb (II and III), the oxime
(V & VIII) and the nitrile (X & XIV). Analysis of urine showed
the same metabolites to be present (Dorough et al., 1970).

When applied to cotton plants or to the soil, aldicarb was
metabolized to the sulfoxides of aldicarb (II), the oxime (VIII)
the nitrile (X), the amide (XI), the alcohol(IX), and the acid
(XII);to the sulfones of aldicarb (III), the oxime (V), the
alcohol (VI), and the acid (XIII). Conjugates of compounds IV,
VI, X and XIII were also observed (Bartley et al., 1970).

The fate of aldicarb was studied in sand, loam, clay, and muck
soils. Within the range of pH 6 to 8, no important differences
could be attributed to pH. Fifty percent moisture was optimal
for oxidation of aldicarb to the sulfoxide and sulfone. A faster
rate of decomposition to non-toxic products occurred at a moisture
level of 100%. Volatilization of aldicarb increased with increased
water evaporation. The half-life of all toxic compounds exceeded
56 days (Bull et al., 1970).

Toxic	Non-toxic
Aldicarb sulfoxide	oxime sulfoxide
Aldicarb sulfone	oxime sulfone
	nitrile sulfoxide
	nitrile sulfone

Radiolabeled aldicarb was applied in-furrow at the rate of 3 lbs.
per acre at the time of planting potatoes. Soil samples taken
immediately after application of aldicarb showed an average
initial residue level of 13.1 ppm of total ^{14}C-aldicarb equivalents.
After 7 days, only 26.5% of the initial residue was found in the
soil and 0.5% after 90 days. Although the purity of applied
aldicarb was 98.5%, samples taken within 30 minutes of application
contained 12.7% of the recovered radioactivity as aldicarb
sulfoxide and traces of aldicarb sulfone, oxime sulfoxide and
an unidentified residue. Seven days after application, 48% of
the recovered radioactivity was as aldicarb sulfoxide. Accumulation
in the soil of hydrolytic products of aldicarb sulfoxide and sulfone

was a slow process. Small quantities of oxime sulfoxide and nitrile sulfoxide were detected throughout the 90-day test period. Small quantities of nitrile sulfone were also found but no oxime sulfone. In noncultivated soil, the transformation products of aldicarb isolated from the soil were qualitatively similar to those previously found in cultivated soil (Andrawes et al., 1971a).

Aldicarb was injected into the stems of potato plants. In the early stages of plant growth sulfinyl prevailed; during the maturation of the plant, the sulfonyl prevailed. Subsequent oxidation yielded the corresponding aldehydes. Treatment of tuber buds showed that conjugates of the propanols constituted the major portion of the water-soluble metabolites in the tuber (Andrawes et al., 1971b).

To study the fate of aldicarb in laying hens, single oral doses were administered. Approximately 80 % of the dose was excreted in two days. At 10 days, 90% of the dose had been excreted. In the feces, compounds II, III,IV, V, VI, VII, VIII, IX, X and XIV were found as well as water-solubles and unextractables. Residues in tissues showed a similar qualitative pattern. However, the aldicarb-NCH_2OH (IV) and several unidentified compounds found in the feces were not seen (Hicks et al., 1972).

METABOLITES FORMED

Compound	Hens	Cows	Rat	Cotton	Potato	Flies	Boll Weevil	Soil	Tobacco Budworm
II	+	+	+	+	+	+	+	+	+
III	+	+	+	+	+	+	+	+	+
IV	+								
V	+	+	+	✦	+		+		+
VI	+			+	+				
VII	+		+			+			
VIII	+	+	+	+	+		+	+	+
IX	+			+	+				
X	+	+	+	+	+			+	+
XI				+	+				
XII				+	+				
XIII				+	+				
XIV	+	+	+		+			+	+
XV									+
XVI									+

An $NADPH_2$-requiring larval enzyme from resistant Culex fatigans metabolized aldicarb to the sulfone, sulfoxide, oxime sulfone and sulfoxide, nitrile sulfoxide, and 3 unknowns (Shrivastava et al., 1971).

Aldicarb metabolic pathway diagram showing:

Aldicarb (I): $CH_3-S-C(CH_3)_2-CH=N-O-C(=O)-N(H)(CH_3)$

Aldicarb Oxime (VII): $CH_3-S-C(CH_3)_2-CH=NOH$

Aldicarb Sulfoxide (II): $CH_3-S(=O)-C(CH_3)_2-CH=N-O-C(=O)-N(H)(CH_3)$

[bracketed intermediate]: $CH_3-S-C(CH_3)_2-CH=N-O-C(=O)-N(H)(CH_2OH)$

[bracketed intermediate]: $CH_3-S(=O)-C(CH_3)_2-CH=N-O-C(=O)-N(H)(CH_2OH)$

Aldicarb Sulfone (III): $CH_3-S(=O)_2-C(CH_3)_2-CH=N-O-C(=O)-N(H)(CH_3)$

Aldicarb N-demethyl Sulfoxide (XV): $CH_3-S(=O)-C(CH_3)_2-CH=N-O-C(=O)-NH_2$

Aldicarb N-CH₂OH Sulfone (IV): $CH_3-S(=O)_2-C(CH_3)_2-CH=N-O-C(=O)-N(H)(CH_2OH)$

Oxime Sulfoxide (VIII): $CH_3-S(=O)-C(CH_3)_2-CH=NOH$

Aldicarb N-demethyl Sulfone (XVI): $CH_3-S(=O)_2-C(CH_3)_2-CH=N-O-C(=O)-NH_2$

Oxime Sulfone (V): $CH_3-S(=O)_2-C(CH_3)_2-CH=NOH$

[bracketed]: $CH_3-S(=O)-C(CH_3)_2-CHO$

Nitrile Sulfoxide (X): $CH_3-S(=O)-C(CH_3)_2-CN$

Nitrile Sulfone (XIV): $CH_3-S(=O)_2-C(CH_3)_2-CN$

[bracketed]: $CH_3-S(=O)_2-C(CH_3)_2-CHO$

Sulfoxide Alcohol (IX): $CH_3-S(=O)-C(CH_3)_2-CH_2OH$ → Conj.

Sulfoxide Amide (XI): $CH_3-S(=O)-C(CH_3)_2-C(=O)-NH_2$

Sulfone Amide: $CH_3-S(=O)_2-C(CH_3)_2-C(=O)-NH_2$

Sulfone Alcohol (VI): $CH_3-S(=O)_2-C(CH_3)_2-CH_2OH$ → Conj.

Sulfoxide Acid (XII): $CH_3-S(=O)-C(CH_3)_2-C(=O)(OH)$

Sulfone Acid (XIII): $CH_3-S(=O)_2-C(CH_3)_2-C(=O)(OH)$

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Aldrin, Dieldrin, Isodrin, and Endrin; HCE and HEOM

Aldrin

1,8,9,10,11,11-Hexachloro-2,3-7,6-endo-2,1-7,8-exo-tetracyclo
[6.2.1.1^{3,6}.0^{2,7}]dodec-4,9-diene

Dieldrin

1,8,9,10,11,11-Hexachloro-4,5-exo-epoxy-2,3-7,6-endo-2,1-7,8-exo-
tetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodec-9-ene

Isodrin

1,8,9,10,11,11-Hexachloro-2,3-7,6-endo-2,1-7,8-endo-tetracyclo
[6.2.1.1^{3,6}.0^{2,7}]dodec-4,9-diene

Endrin

1,8,9,10,11,11-Hexachloro-4,5-exo-epoxy-2,3-7,6-endo-2,1-7,8-endo-
tetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodec-9-ene
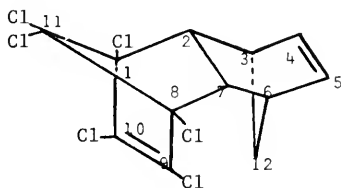
Aldrin
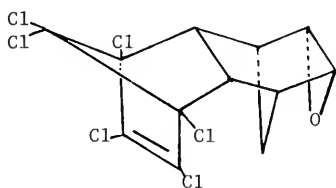
Dieldrin
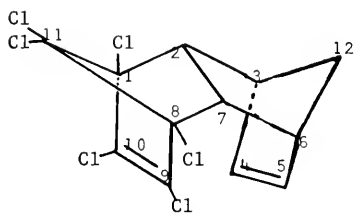
Isodrin
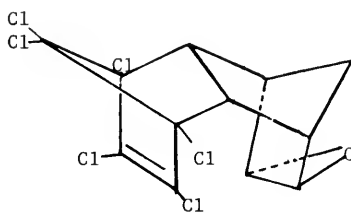
Endrin

<u>HEOM</u>

1,8,9,10,11,11-Hexachloro-4,5-epoxy-2,3-7,6-<u>endo</u>-tricyclo[6.2.1.0^{2,7}]
undec-9-ene

<u>HCE</u>

1,8,9,10,11,11-Hexachloro-3,4-epoxy-2,3-7,6-<u>endo</u>-tricyclo[6.2.1.0^{2,7}]
undec-9-ene

Several configurations for these two compounds are possible. The
configurations are used merely to indicate the relationship to dieldrin
and may require reassessment.

HEOM   HCE

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1,2 XII

Aldrin Chlorohydrin

X

Photoaldrin Chlorohydrin

VIII

III

UV (AIR)

UV

VII

IX

UV (Hexane)

Photodieldrin VI

UV

Aldrin I

1,2,3 4

Dieldrin IV

1,2,4

XIV

UV

1

Photodieldrin VI

1,2

Algae

1,2,4

XV

XI

XII

XVI

Glucuronide

Glucuronide XIII

Aldrin

Glucuronide

1=Mammals   3=Plants
2=Insects   4=Microorganisms

11
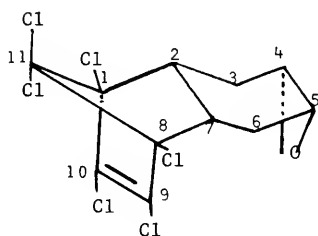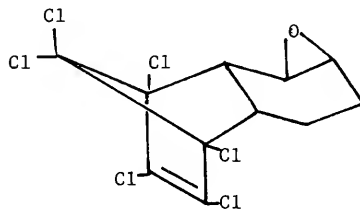
Aldrin epoxidase activity was demonstrated in vitro in three bean species (Phaseolus vulgaris L., Dwarf variety; Vicia fabs L., Broad Bean Long Pod variety; and Phaseolus aurens Roxib., Mung Bean) and in three pea varieties (Pisum sativum L., Alaska Wilt Resistant; Miragreen; and Little Marvel). Although also observed with extracts of two corn varieties (Zea mays L., Golden Bantam and PAG-SX29) the activity was much less than in the beans and peas. In all cases activity was greater in the microsomal fraction than in the 105000g soluble portion. It was also observed that NADPH stimulated exoxidation and that broad bean root extracts inhibited preparations from peas or Dwarf bean roots. The inhibitory activity was in the 105000g soluble fraction (Mehendale et al., 1972). On a weight basis, pea root homogenates were less than one-half as active as bean. The oxidase system was most active at pH 6.5 and a seedling age of 9 to 21 days. Small amounts of a compound chromatographically similar to aldrin diol was also observed. When dieldrin was the substrate instead of aldrin, no diol was observed (Yu et al., 1971). In addition to the cis- and trans-dihydroaldrins, an aldrin alcohol was also detected (Mehendale and McKinney, 1972).

Subcellular fractions, obtained from peas, epoxidized aldrin to dieldrin. The enzymes in peas appeared to be different than those in animal tissues. Instead of microsomal origin, in pea roots most of the activity was found in the soluble fraction. The pea root enzyme(s) appeared to be specific for aldrin and did not epoxidize either isodrin (the endo-endo isomer of aldrin) or heptachlor (Lichtenstein and Corbett, 1969).

Seeds of carrots and onions were treated with aldrin. Aldrin, but no dieldrin, was found in the periderm tissue of carrots. In onion, thin layer chromatography indicated complete transformation of aldrin to dieldrin (Hullpke, 1969). After foliar application of aldrin no white cabbage, six metabolites including dieldrin, photodieldrin (VI), and an unidentified hydrophylic compound were found. Application of dieldrin also gave rise to photodieldrin and other hydrophylic products. Conversion rates of aldrin and dieldrin after soil application to carrots, spinach and white cabbage were lower than after foliar application (Weisgerber et al., 1970).

Extensive work is being conducted to obtain information on the microsomal enzymes of insect species and their respective detoxification systems. In larvae of the southern armyworm (Prodenia eridania), maximum activity of an epoxidase has been associated primarily with the mid-gut (Krieger and Wilkinson, 1969). Activity reaches a maximum in the sixth instar. A similar system was found in lepidoptera larvae but was not localized (Williamson and Schechter, 1970). Housefly microsomal oxidase was found to be capable of aldrin and photoaldrin epoxidation and oxidative dechlorination of photodieldrin to Klein's metabolite and to water soluble metabolites (Khan et al., 1970). Rabbit and pig liver microsomes hydrated aldrin to dihydroxy-aldrin (Brooks et al., 1970).

About 45% of the labeled aldrin applied to algae (<u>Chlorella pyrenoidosa</u>) in nutrient solution was observed in extracts of the algae. Only 3% of the label remained in the nutrient salt solution. The remainder of the radioactivity was not extractable. After chromatography, synthesis and mass spectroscopy, the radioactive material extracted from the algae was identified as 1,2,3,4,9,9-hexachloro-1,4,4a,5,6,7,8,8a-octahydro-1,4-methanonaphthalene (Elsner et al., 1972).
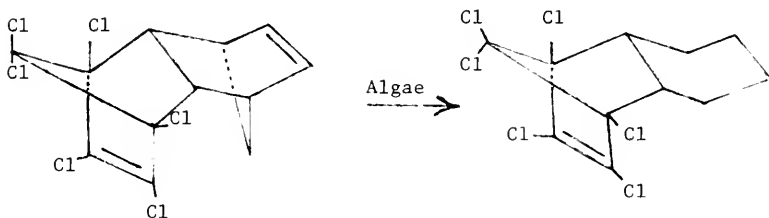
Fresh water invertebrates converted aldrin to dieldrin. This <u>in vivo</u> epoxidation was found in algae, protozoa, coelenterates, worms, arthropods, and molluscs and indicated the presence of microsomal mixed-function oxidases. The rate of conversion of aldrin to dieldrin showed considerable variation: Hydra, <u>Dugensia</u> sp., Leech and <u>Asellus</u> sp. <u>Gammarus</u> sp., <u>Daphnia</u> sp., <u>Cyclops</u> sp., and <u>Cambarus</u> sp. <u>Anadonta</u> sp., <u>Lymnaea</u> sp., and <u>Aeschna</u> sp. <u>Aedes</u> sp. (Khan et al., 1972). Aldrin was also converted to dieldrin in the ostracod (<u>Chlamydotheca arcuata</u>). No further metabolism occurred and dieldrin slowly accumulated (Kawatski and Schmulbach, 1971).

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In studies with 20 microbial cultures which had been shown to degrade dieldrin, 13 degraded aldrin. Only aldrin trans-diol was identified from aldrin metabolism. Several species of trichoderma and pseudomonas, as well as one each of micrococcus and bacillus, were identified (Patil et al., 1970).

After addition of aldrin to soil samples, a water-soluble dicarboxylic acid was isolated. After preparative isolation and methylation, gas chromatography, mass spectrometry, and infra-red spectroscopy showed the material to be identical with authentic dihydrochlordendicarboxylic acid dimethyl ester (Moza et al., 1972).

When exposed to Fenton's reagent, aldrin was converted to dieldrin (Marshall and Wilkinson, 1970).

Dieldrin was fed to white rats. Two metabolites were isolated from feces and two from urine. The minor fecal and urinary metabolites behaved chromatographically the same as trans-dihydroxydihydroaldrin (XVI). The urinary metabolite has been identified as the ketone (XII). Compound (XI) was conjugated to form the glucuronide (XIII). When the conjugation system became a limiting factor, then the ketone (XII) was formed. A microsomal fraction from rabbit or rat liver conjugated trans-aldrindiol (XVI) (Matthews and Matsumura, 1969). In other studies with microsomes and liver slices, the trans-aldrindiol formed very slowly (Brooks and Harrison, 1969). The half-life of dieldrin was 10.3 and 3.0 days in adipose and brain tissue, respectively. In blood and liver, there was two phases: a rapid depletion ($t_{1/2}$=1.3 days) and a slower elimination ($t_{1/2}$= 10.2 days)(Robinson et al., 1969).

In other studies when labeled dieldrin was fed to rats, ten times as much radioactivity was excreted in feces as in urine; and three to four times as much radioactivity was found in feces from males as from females. Klein's metabolite was the only dieldrin metabolite found in any organ or tissue of males toher than stomach and intestines. In vitro an hydroxylated metabolite was observed which readily conjugated to form the glucuronide (Matthews et al., 1971). This metabolite has been found to be the major metabolite in feces and identified as the syn-hydroxydieldrin (XIV) (McKinney et al., 1972a,b).

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Other studies have also shown that microsomes from the pig and rat rapidly metabolize HEOM by cleavage and hydration of the epoxide ring to a <u>trans</u>-dihydrodiol (Brooks and Harrison, 1964; Brooks, 1966). Strong

Dieldrin   Aldrin <u>trans</u>-diol

HEOM   HEOM <u>trans</u>-diol

HCE   HCE <u>trans</u>-diol
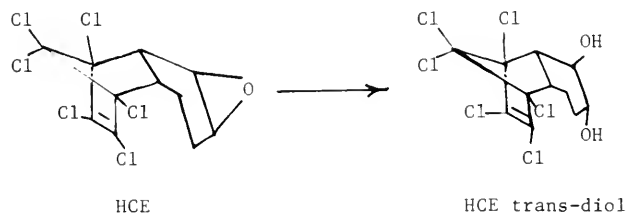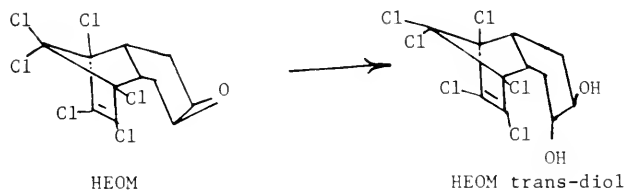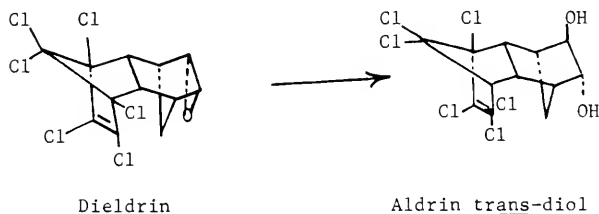
interspecific differences in metabolic capacity have been shown. Using liver microsomes, the per cent hydration of HEOM was as follows:

Rabbit	98%	Fowl (<u>Gallus domesticus</u>)	65%
Rat	94	Quail (<u>Coturnix coturnix</u>)	16
Rook (<u>Corvus frugilegus</u>)	92	Fulmar(<u>Fulmaris glacialis</u>)	13
Jackdaw (<u>Corvus monedula</u>)	90	Pigeon(<u>Columba palumbus</u>)	4

No evidence for an endogenous inhibitor in pigeon liver was found (Zorgani et al., 1970).

Dieldrin metabolism in the CFE rat and CFI mouse were similar.   In
both species, a fecal metabolite was indentified as the trans-
dihydroaldrindiol and in urine a dicarboxylic acid was found.   This
same acid has been identified as a metabolite of the diol after
oral doses to rats.   The major metabolite in both rat and mouse was
hydroxydieldrin (XIV).   Mouse urine contained an unidentified
metabolite.   Rat urine contained a pentachloroketone and an unidentified
compound (Baldwin and Johnson, 1972; Oda and Mulelr, 1970).

Liver microsomes from rabbits and pigs readily hydrated the dieldrin
analogs HEOM and HCE to their respective dihydroxy products (Brooks,
1969).

After feeding labeled dieldrin to sheep, six metabolites were found
in urine.   Two were water soluble.   Evidence indicated that one was
a glucuronic acid conjugate of the trans-diol and the other a conjugate
containing glucuronic acid and possibly glycine.   The other four
were hexane soluble.   One has been identified as the trans-diol after
spectral comparison with an authentic sample.   The other was identified
by chemical and spectral means as syn-epoxy-hydroxydieldrin (XIV)
(Hedde et al., 1970; Feil et al., 1970).   In studies with rats fed
a diet containing dieldrin, a compound was isolated from urine and
identified as the pentachloro-epoxy-ketone (XII).   Another metabolite
isolated from rat feces was identified as the hydroxy analog of the
cage form of dieldrin (XI) (Richardson et al., 1968).   In other
studies, a hydroxy compound was isolated and identified as compound
XIV (Baldwin et al., 1970) in rat (Baldwin et al., 1970) and human
feces (Richardson and Robinson, 1971).

After exposure of the sailfin mollie (Poecilia latipinna) to low
levels of dieldrin, two unidentified compounds were found in extracts
of the liver and various organs (Lane et al., 1970).

The transfer of dieldrin from environmental water into the vascular
system of isolated perfused gills of rainbow trout occur only when
protein (probably lipoprotein) was present in the perfusion fluid
(Fromm and Hunter, 1969).

During midget penetration of dieldrin in Blaberus discoidalis,
Manduca sexta, and Mus musculus, dieldrin underwent very little
metabolism.   Two unidentified metabolites were observed (shah
and Guthrie, 1970).

Houseflies hydrated the epoxide ring of the dieldrin analog HEOM
rapidly to the trans-diol.   Housefly microsomes also effected
this change.   HCE was also metabolized fairly rapidly by houseflies.
The HCE epoxide ring was hydrated more slowly than that of HEOM by
housefly microsomes (Brooks, 1969).

Dieldrin was applied to two small watersheds to a depth of 7.5 cm. Analyses indicated that the major pathways of dieldrin loss were by volatilization and sediment transport. Largest losses occurred during the first 2 months after application. Dieldrin residues were found in maize plants grown in the treated soil, as well as in the runoff water (Caro and Taylor, 1971).

Some studies indicated that soil microorganisms and wheat plants metabolized dieldrin to little, if any, extent (Saha and Lee, 1970). It was also found that adsorption of dieldrin was greater with dead yeast than living yeast. Adsorption isotherms were best described by Freundlich's equation (Voerman and Tammes, 1969):

$$C_y = kc_e^n \quad \text{in which } n = 1$$

$$C_y = \text{concentration in yeast}$$

$$C_e = \text{equilibrium concentration in water}$$

The soil fungus <u>Trichoderma</u> <u>koningi</u> was inoculated into a culture tube. ^{14}C-Dieldrin, labeled at all chlorine attached carbons, was aseptically inoculated into the fungal culture. After 17 days, an average of 3.1% of the radioactivity was evolved as ^{14}CO$_2$ (Bixby et al., 1971).

About half of 175 bacterial strains isolated from soil produced ^{14}CO$_2$ and water-soluble dieldrin metabolites in culture. A summary of the number of strains giving positive results per number tested is summarized (Jagnow and Haider, 1972).

<u>Pseudomonas</u> sp.	10/24
<u>Corynebacterium</u> sp.	22/44
<u>Arthrobacter</u> sp.	19/35
<u>Mycobacterium</u> sp.	24/47
<u>Nocardia</u> sp.	8/15
<u>Mycococcus</u> sp.	3/5
<u>Micrococcus</u> sp.	1/1
<u>Bacillus</u> sp.	1/1
Yeasts	3/3
Total	91/175

Photodieldrin and hydrophylic compounds were found in soil from dieldrin treated fields (Lichtenstein et al., 1970). Photodieldrin has been isolated from culture media after incubation of dieldrin with microorganisms from such diverse environments as soil, lake water, rat intestines and cow rumen (Matsumura et al., 1970).

Dieldrin

hν →

Photodieldrin

hν

hν

Aldrin Chlorohydrin

hν →

Photoaldrin Chlorohydrin

(Lombardo et al., 1972)

18
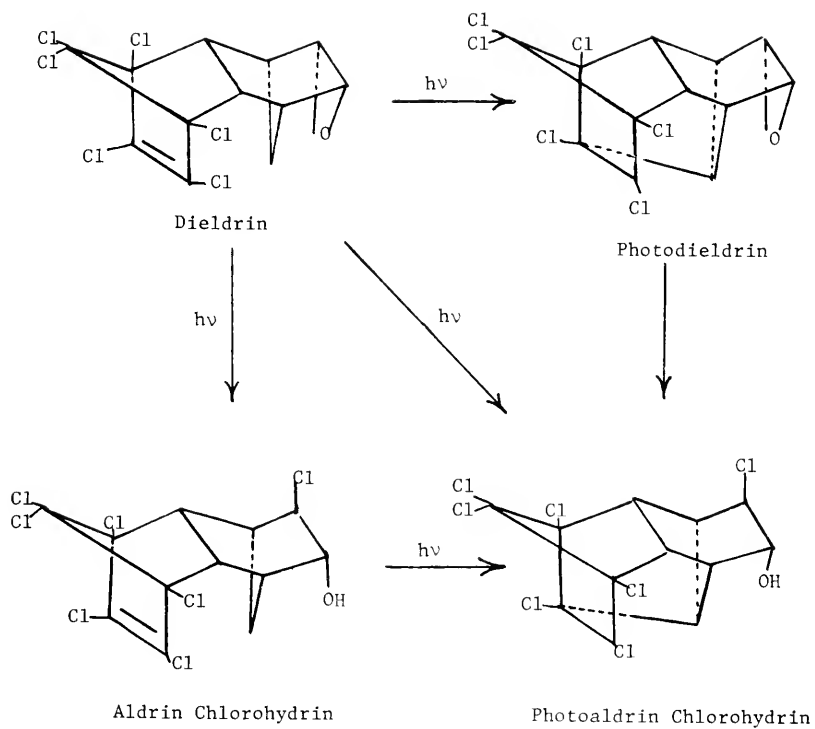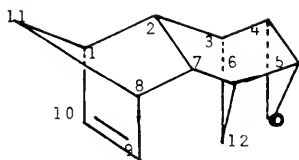
For Compounds I to V

Below

I. 1,8,9,10,11,11-Hexachloro-

II. 1,7,8,9,10,11,11-Heptachloro-

III. 1,8,9,10,11,11-Hexachloro-7-nitro-

IV. 1,8,9,10,11,11,Hexachloro-7-hydroxy-

V. 1,8,9,10,11,11-Hexachloro-7-ONO_2-
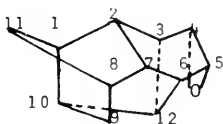
For Compounds VI to IX

Below

VI. 1,4,8,10,11,11-Hexachloro-5-hydroxy-9-keto-

VII. 1,8,9,10,11,11-Hexachloro-7,9-dinitro-

VIII. 1,8,10,11,11-Pentachloro-9-keto-

IX. 1,8,9,10,11,11-Hexachloro-

$$\text{Dieldrin} \xrightarrow[\text{Freon 51-12, NO}_2]{h\nu(\lambda > 300 \text{ nm})} \text{Cmpds III to VII}$$

$$\xrightarrow[]{h\nu \quad CCl_4, NO_2} \text{Cmpds II to VI}$$

$$\xrightarrow[h\nu]{O_3, \quad \text{Freon 51-12}} \text{Cmpds IV}$$

$$\xrightarrow[]{\cancel{h\nu \; NO_2, \; Air}} \text{Cmpd IX}$$

$$\text{Cmpd VI} \xrightarrow[]{h\nu} \text{Cmpd VIII}$$
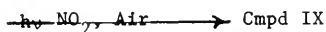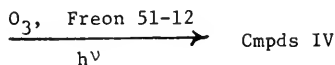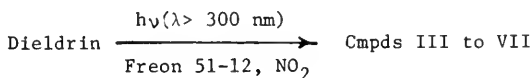
Photoaldrin and photodieldrin have been produced by direct action of sunlight and ultraviolet light on aldrin and on solid and dissolved dieldrin (Benson, 1971; Fischler and Korte, 1969; Geike, 1970). Thin film irradiation of dieldrin produced a compound identified as photoaldrin chlorohydrin (Lombardo et al., 1972).

Irradiation of dieldrin in n-hexane or methanol-water with UV yielded 3 dechlorination products besides the known photoproducts of dieldrin. In addition to the cage-like dieldrin isomer photodieldrin and the monodechlorinated dieldrin, three new compounds were identified as the mono- and di-dechlorinated "cage" isomers and the di-dechlorinated dieldrin (Nagl et al., 1970). Three crystal forms of photodieldrin melted at 184, 194, & 197°C(Lombardo, 1969). Dieldrin was also irradiated in atmospheres containing NO_2 and ozone. This is summarized in the accompanying figure (Nagl and Korte, 1972).

Irradiation of the dieldrin alcohol or ketone gave rise to two isomeric alcohols and ketones, respectively (Bieniek and Korte, 1969).

After intravenous administration of labeled photodieldrin into rats, radioactivity excreted in 72 hours by male rats amounted to 15.2% in feces and 1.5% in urine; by female rats, 14.9% in feces and 0.4% in urine. About 95% of the excreted radioactivity was in the form of two metabolites. One was more polar, the other less polar, than photodieldrin. Rabbits excreted more labeled material in urine than in feces after application of photodieldrin. The radioactivity was mainly as a very polar metabolite (Klein et al., 1969). When photodieldrin was fed to Carworth Farm rats (type E), in addition to unchanged photodieldrin, a second compound was observed after gas-liquid chromatography of tissue extracts. Infrared and mass spectrometry were used to identify this metabolite as the 12-keto analog of photodieldrin. This compound is identical to the rat urine keto metabolite of dieldrin (XII) (Baldwin and Robinson, 1969). In other studies, when rats were fed ^{14}C-photodieldrin over a period of 12 weeks, the principal metabolite in the male rat urine was identified as the ketodieldrin known as Klein's metabolite. Other metabolites were believed to be present. In urine of the female rat, no ketodieldrin was observed. However, four other metabolites, very polar and non-volatile, were observed but not identified. No photodieldrin was observed in urine of either sex (Klein et al., 1970). Male rats excreted a greater amount of photodieldrin than did female rats. The latter stored 3 to 10 times more ^{14}C-activity than males (Dailey et al., 1970).

When larvae of Aedes aegypti were treated with photodieldrin, two metabolites were observed. One was very hydrophylic; the other, less hydrophylic than photodieldrin (Klein et al., 1969). The 12-keto compound has been identified in insects (Khan et al., 1969).

After application of photodieldrin to cabbage, one strongly hydro-phylic and two lesser hydrophylic metabolites were observed (Klein et al., 1969).

Incubation of photodieldrin with Aspergillus flavus and Pencillium notatum gave rise to two metabolites, one strongly hydrophylic and the other less hydrophylic (Klein et al., 1969).

Houseflies metabolized isodrin to endrin. Sesamex acted as a synergist (Khan et al., 1970a).

When isodrin was incubated with homogenates from excised roots of bean seedlings (Phaseolus vulgaris, Dwarf Horticulture variety), a compound corresponding chromatographically to endrin ketone (also referred to as Δketo endrin) was observed. A second metabolite, present in a very small amount, was observed but not identified. No endrin was found. Similar studies with pea root homogenates indicated that the enzyme systems present were less than half as active in the bean (Yu et al., 1971).

Exposure of isodrin to ultraviolet light gives rise to a "birdcage" isomer which is less toxic than the parent compound (Rosen et al., 1969). This photoisodrin is incapable of epoxidation and oxidative dechlorination by houseflies to a ketone but can be hydroxylated. Position of the hydroxyl was not indicated (Khan et al., 1970a & b).

Rats metabolized endrin to at least three compounds. One, found in tissues and urine, was identified by chemical, chromatographic, and spectral means as the keto endrin. Two monohydroxylated endrin analogs have been found in feces but not in tissues. One has been identified as the hydroxy endrin, the hydroxyl group endo with respect to the epoxy group. The second compound was not identified (Richardson et al., 1970; Baldwin et al., 1970). In studies with perfused rat livers, endrin was metabolized to an unidentified hydrophylic compound. The rate of metabolism was greater with livers from males than females (Altmeier et al., 1969).

When exposed to endrin, susceptible and resistant third instar larvae of the tobacco budworm (Heliothis virescens Fabricus) metabolized endrin to two metabolites identified as the endrin-aldehye and ketone. Resistant insects produced two additional metabolites not identified (Polles, 1972).

Twenty microbial cultures, including species of trichoderma, pseudomonas, micrococcus, arthrobacter, and bacillus were found capable of degrading endrin. Only keto endrin was identified (Patil et al., 1970).

Other studies have shown that, when applied to air-dried soils at room temperatures, endrin can decompose by isomerization to an aldehyde and a ketone (Asai et al., 1969).

About 150 isolates from soils were screened for their ability to degrade endrin. Of these, twenty-five were active and the conversion of endrin into keto endrin (metabolite IV) (Δ-keto endrin) was common to all of these cultures. One culture (yeast) produced only the keto endrin. Using a culture of _Pseudomonas_ sp., the presence of six additional metabolites was demonstrated. Spectroscopic studies indicated the presence of a compound with 5 chlorines and a carbonyl group. The -ClC=CCl- and epoxy groups were apparently not present and the infrared spectrum was almost identical to that of the endrin aldehyde studied by Philips et al., 1962. Spectral studies of a second metabolite indicated aldehydic structure similar to that of the previously mentioned pentachloro-ketone but with an extra chlorine atom. Another metabolite from mass and infrared spectra appeared to be similar to Δ-keto endrin. In view of the presence of I.R. peaks indicating the presence of -ClC=CCl- and a carbonyl group, it was felt that this was a non-bridged ketone.

The sixth metabolite apparently contained six chlorines. The fragmentation pattern shown in the mass spectrum closely resembled that of keto endrin; and the I.R. indicated the presence of a carbonyl group (Matsumura et al., 1971).

Twelve weeks after application of ^{14}C-endrin to upper leaf surfaces of cotton plants, 33 percent of the applied radioactivity was recovered, 26 percent on and in the leaves and the remainder in the plant parts and soil. At least 5 products were present in addition to unchanged endrin. Two compounds were only slightly less hydrophylic than endrin. Three other very hydrophylic compounds were observed. One was identified as endrin ketone. A second compound, not identified, had a higher molecular weight (as indicated by mass spectrometry) and contained the chlorinated frame of endrin (Bayless et al., 1970).

In cyclohexane or hexane solutions, endrin was converted to the half-cage ketone when irradiated at 253.7 nm, 300 nm, or in sunlight. This keto endrin was also found in a muck soil which had been treated with endrin for 5 years at the rate of 2 lbs. per acre (Zabik et al., 1970, 1971). In addition to the pentachloro ketone, bicyclohexyl was produced with cyclohexane solutions. Intermediates in the ketone formation were monodechloro endrin and a half-cage pentachloro alcohol (McBee and Burton, 1972).

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Rat liver microsomal preparations were incubated with dihydoisodrin. The major metabolite was isolated and identified as 6-_exo_-hydroxy-6,7-dihydroisodrin. Two other metabolites were observed but not identified. Similar results were obtained with microsomal enzymes from southern armyworm larval gut, and liver preparations of pig, mouse, pine vole and American kestrel (Krieger and Wilkinson, 1971).

Isodrin (I)

Keto Endrin (IV)

OH⁻
Δ

UV

2,
5,6

1,2,3,4

Endrin Aldehyde

2, 4

1
2,3,4

Endrin(epoxi)(II)

Hydroxy Endrin(III)

H⁺ or
Δ

hν
Methanol

cyclohexane

hν

1
4 / UV

1=Rat
2=Insect
3=Soil
4=Plant
5=Plant homogenates
6=Animal homogenate

24
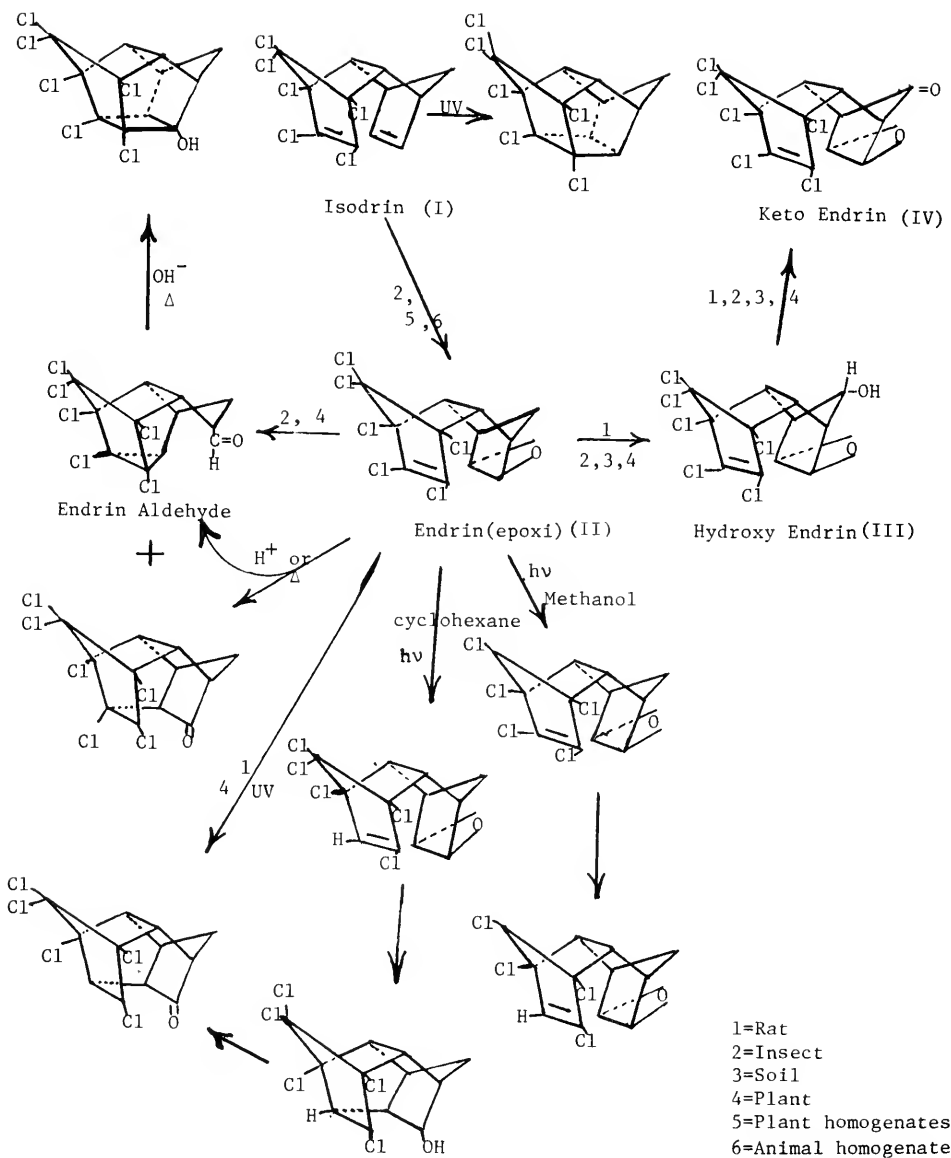
<u>AMIBEN</u> [3-Amino-2,5-dichlorobenzoic acid]

The amide and methyl ester of amiben underwent rapid hydrolysis
in soil. In moist soil the half-life was 2.9 days for the methyl
ester, 7.5 days for the hydroxypropyl ester, and more than 16 days
for the butoxyethyl ester (Talbert et al., 1970).

When morningglory and velvetleaf were exposed to amiben, amiben
binding occurred at a near-linear rate in both species but the
amount bound was a small portion of total absorbed. N-glucosyl
amiben synthesis initially lagged but then proceeded more rapidly
in the morningglory. In contrast, free amiben accumulated to a
higher level in velvetleaf (Stoller, 1969).

Amiben was fed to a holstein cow. Urine and manure was collected
and analyzed. Amiben appeared as the free acid and as the
conjugated acid. Amiben residues were absent in milk samples.
The herbicide was stable when incubated with rumen fluid for
24 hours   (St. John, Jr., and Lisk, 1970).

In plants, amiben is converted to the $\underline{N}$-glucosylamine. The
enzyme, isolated from soybeans, was found to be specific for
uridine diphosphate-5'glucose and the corresponding thymidine
analog. The K_i constant for uridinediphosphate (UDP) was $4.84 \times 10^{-4} M$
(Frear, 1967 & 1968; Frear et al., 1967).

AMINOCARB (Matacil) [N-Methyl-4-dimethylamino-3-methylphenyl carbamate]

Very little CO_2 was produced when liver enzymes were incubated with Aminocarb. Although the same major metabolites were observed with human and rat liver, there was a decrease in production of products by human liver as compared with rat liver. Three metabolites were identified as the monodesmethyl and di-desmethyl aminocarb and the N-hydroxymethyl analogs (Strother, 1970 & 1972).
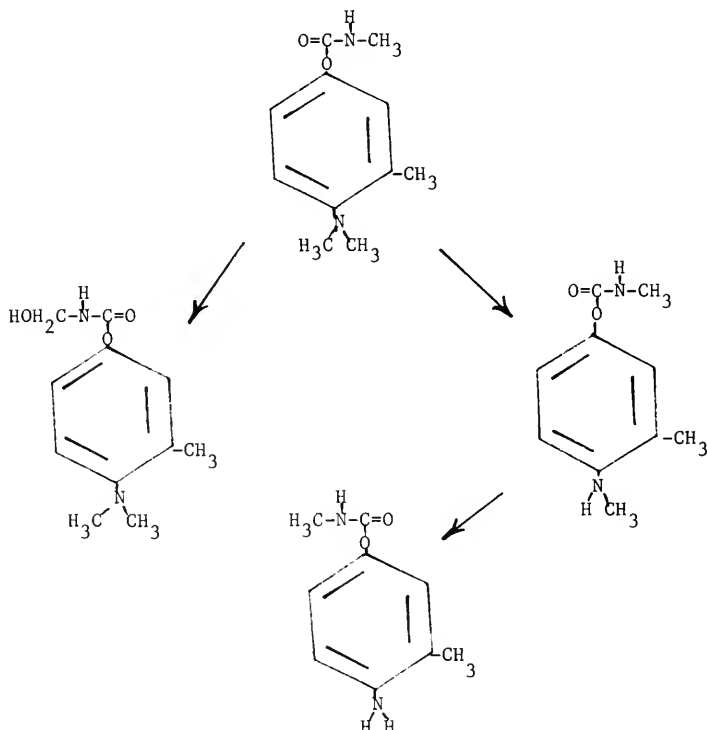
AMITROLE (AT, ATA, 3-AT, Aminotriazole) [3-Amino-1,2,4-triazole]

Excised leaves of Canada thistle (Cirsium arvense L.) and bean
(Phaseolus vulgaris L.) metabolized amitrole to the same products,
but at different rates. Compound I, probably the alanine analog,
was produced about 3 times faster by bean leaves than by thistle
leaves. However, Canada thistle converted Compound I to an
unidentified compound about 10 times faster than did bean
(Smith et al., 1968).

Amitrole degraded in soils treated with potassium azide and
ethylene oxide. Addition of EDTA-Na to soil treated with ethylene
oxide reduced amitrole degradation. When autoclaved soil was
re-inoculated with mixed cultures of soil microorganisms isolated
from soil in which amitrole had been rapidly degraded, only slight
degradation occurred. Amitrole degradation also increased when $FeSO_4$
was added to the soil (Kaufman et al., 1968).

In couch grass (Agropyron repens) exposed to ATA, two unidentified
metabolites were observed (Fiveland et al., 1972).

ANILINES

The discovery that azobenzenes and other polyaromatic molecules containing condensed aniline moieties could arise during the degradation of many pesticides has created a unique situation of considerable concern. The studies described have significance with respect to (but not limited to):

All Ureas
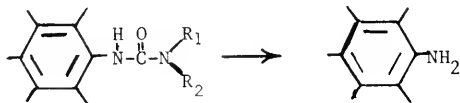
N-Phenyl Carbamates (N-Phenyl Amides, Carbanilides)
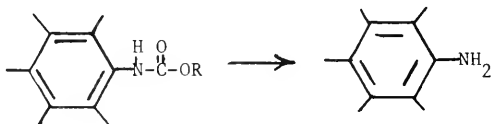
CEPC
Chlorpropham
Dicryl
Karsil
Propanil
Propham
SWEP

Misc. Compounds (Compounds that may give rise to aniline derivatives.)

Dichloran
PCNB
TCNB
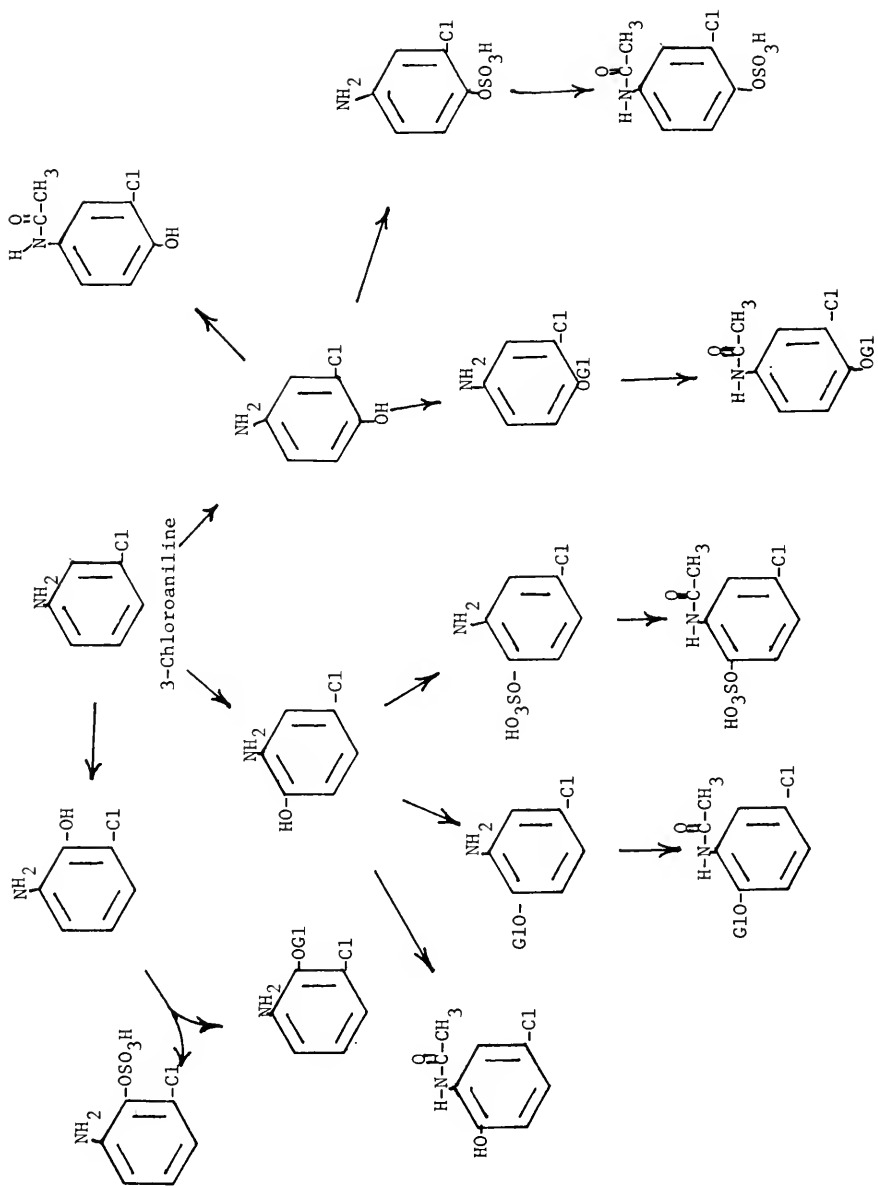
The metabolic fate of 3-chloroaniline was studied in male albino rats. After a single oral dose, urine was collected and analyzed. After heating with HCl, the urine was neutralized and chromatographed. TLC showed the presence of 2-amino-4-chlorophenol and 4-amino-2-chloro-phenol. Through I.R. and gas chromatography, the acetyl phenols were also identified. Glucuronides and sulfates of the phenols and their acetyl derivatives were also observed. The o-hydroxylated derivative, 2-amino-6-chlorophenol, was not found but traces of the glucuronide and sulfate were observed in several fractions of the ion exchange chromatograph. No hydroxylation meta to the amino group was found (Bohme and Grunow, 1969).

Rabbits, injected with 4-chloroacetanilide or 4-chloroaniline, produced 4-chloroglycolanilide and 4-chlorooxanilic acid. These compounds were excreted via the urine. In pigs, the transformation of 4-chloroglycol-anilide to 4-chlorooxanilic acid does not occur. Incubation of urine with glucuronidase and sulfatase splits the conjugates of 2-hydroxy-4-chloroaniline, a metabolite of 4-chloroaniline. The free hydroxy compound can then condense to form the 3-amino-7-chlorophenoxazone isolated from urine after enzymatic action (Kiese and Lenk, 1971).

Photolysis of 4-chloroaniline in the presence of FMN gave 4,4'-dichloro-azobenzene and 4-chloro-4'-(4-chloroanilino)-azobenzene (Rosen et al., 1970).

When 3,4-DCA was added to a culture of Fusarium oxysporum, 3,3',4,4'-tetrachloroazoxybenzene was isolated (Kaufman et al., 1972).

Under anaerobic soil conditions, disappearance of 3,4-DCA was similar in sterile and non-sterile soil. The rate of disappearance for the first 10 weeks was about 3% per week. Aerobically, about 25% of total disappearance was attributable to biological activity. The amounts of tetrachloroazobenzene (TCAB) produced varied in different soils and with temperature. TCAB reached a maximum in soil at about one week and then declined. By the third week, TCAB had completely dis-appeared (Sprott and Corke, 1971).

Photolysis of 3,4-DCA in the presence of FMN produced TCAB and 4-(3, 4-dichloroanilino)-3,3',4'-trichloroazobenzene. The latter was stable in methanol to light of wavelength greater than 297 nm for 10 hours and to incubation in soil for 2 months (Rosen et al., 1970; Rosen and Siewierski, 1971; Rosen and Winnett, 1969).

UV irradiation of DCA in benzene under nitrogen produced 3,3',4,4'-tetrachloroazobenzene (Plimmer and Kearney, 1969).

Various anilines arise in soil as products of herbicide metabolism. These chloroaniline moieties can then be converted to azobenzene residues. 3-Chloroaniline and 3,4-dichloroaniline condensed to

4-Chloroaniline

Rabbits

FMN
UV

Sulfate

Glucuronide

31

form 3,3,4 –trichloroazobenzene, 3,3'-dichloroazobenzene and 3,3',4,4'-
tetrachloroazobenzene (TCAB) in soil. When propanil and solan were
applied together, three azobenzenes were produced: 3,3'-dichloro-
4,4'-dimethylazobenzene (DCDMAB); 3, 3',4,4'-tetrachloroazobenzene
(TCAB); and 3,3',4-trichloro-4'-methylazobenzene (TCMAB). The
proportion of azobenzene residues was related to rate at which the
aniline moieties were liberated (Bartha, 1969 and 1971).

The intermediate steps in the formation of these azobenzenes by
peroxidases was investigated. To this end 4-chloroaniline and
3,4-DCA were reacted with peroxidase and H_2O_2. The initial attack
produced a chloroanilino free radical. Then the unstable chloro-
phenylhydroxylamine was formed. These condensed with excess
chloroanilines and formed chloroazobenzenes (Bordeleau et al.,
1972). In soil, azoxybenzenes also formed (Bordeleau and Bartha,
1970).

Capacity to transform 3,4-DCA to TCAB was correlated with soil
peroxidase activity. Several bacteria, actinomycetes and fungi
exhibiting peroxidase activity were isolated and characterized
as being Geotrichum sp., Bacillus sp., Arthrobacter sp., Pseudomonas
sp., Streptomyces sp., and Aspergillus sp. Geotrichum candidum
exhibited highest peroxidase activity and was used to obtain two
extracellular enzymes that were active in aniline transformation
(Bordeleau and Bartha, 1972a & b).

| | Activity | |
	Peroxidase	Aniline Oxidase
optimal pH	4.4 – 5.0	4.8 – 5.4
Activation energy(Q_{10})	3.0	1.6
K_m (aniline)	3.1×10^{-4} M	4.4×10^{-4} M
K_m (H_2O_2)	2.4×10^{-6} M	----
K_m (O_2)	----	9.1×10^{-4} M

When 4-chloroaniline was incubated with Geotrichum candidum, 4,4'-
dichloroazobenzene and 4-chloro-4'-(4-chloroanilino)azobenzene were
observed in addition to some unidentified material (Bordeleau and
Bartha, 1972c).

When TCAB was supplied in nutrient solution to roots of rice (Oryza
sativa L.), TCAB was translocated to the shoots. Analyses of plant
residues indicated that no TCAB metabolism occurred in the plants.
When propanil or 3,4-dichloroaniline was used, there was no detectable
TCAB in the plants (Still, 1969).

In other studies, microbial metabolism produced 3,3',4,4'-tetrachloro-azobenzene and 3,3',4,4'-tetrachloroazoxybenzene from 3,4-dichloro-aniline. Several transformations of the amino group occured and included acetylation, formylation and oxidation. Hydroxylation of the aniline ring also occured (Kaufman et al., 1971).

3,4-DCA

3,3',4,4'-Azobenzene   3,3',4,4'-Azoxybenzene
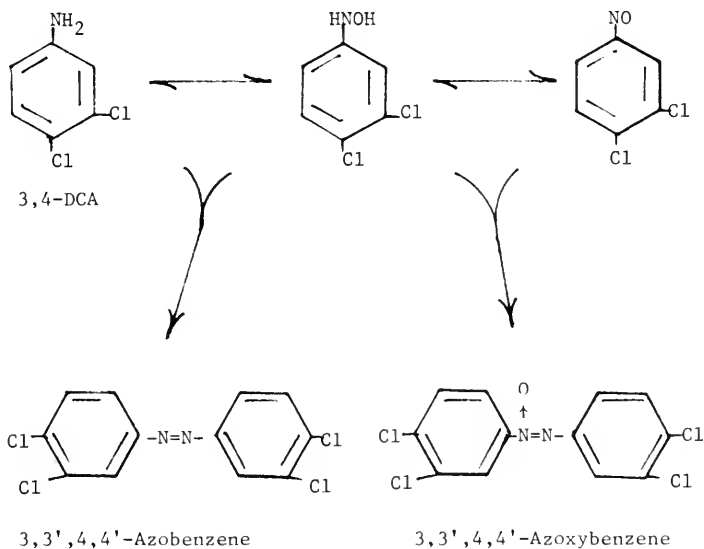
Compound Tested	Transformation by	
	Peroxidase	Aniline Oxidase
Aniline	+	+
2-NO$_2$-Aniline	−	−
3-	−	−
4-	−	−
2-F-Aniline	+	−
3-	+	−
4-	+	+
2-Cl-Aniline	+	−
3-	+	−
4-	+	+
2-I-Aniline	+	−
3-	+	−
4-	+	+
2-CH$_3$-Aniline	+	+
3-	+	+
4-	+	+
2-OCH$_3$-Aniline	★	★
3-	★	★
4-	★	★
2,3-Cl$_2$-Aniline	+	−
2,4-	+	+
2,5-	+	−
2,6-	−	−
3,4-	+	+
3,5-	+	−
3-Cl-2-CH$_3$-Aniline	+	+
2-Cl-6-CH$_3$-	+	−
3-Cl-6-CH$_3$-	+	+
2-Cl-4-CH$_3$-	+	+
4-Cl-2-CH$_3$-	+	+
3-Cl-4-CH$_3$-	+	+
2,3,4-Cl$_3$-Aniline	+	−
2,4,5-Cl$_3$-	−	−
2,4,5-(CH$_3$)$_3$-	+	+
2,4,6-Cl$_3$-	−	−
2,4,6-(CH$_3$)$_3$-	+	+
2,4,6-(OCH$_3$)$_3$-	★	★
2,3,4,5-F$_4$-	−	−
2,3,5,6-F$_4$-	−	−
2,3,4,5,6-F$_5$-	−	−

*Transformation products consisted of colored polyaromatic compounds.

(Bordeleau and Bartha, 1972c).

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ANTIMYCIN

Antimycin A$_1$ $\xrightarrow{k_1}$ Blastmycic acid (I) + Antimycin lactone (II)

$\xrightarrow{k_2}$ Fatty acids
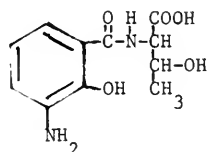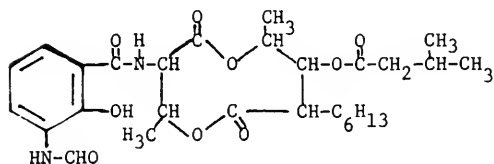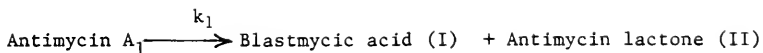
Antimycin A$_1$
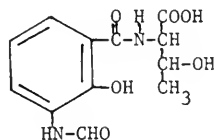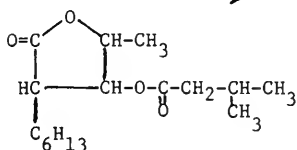
Antimycic acid

Antimycin lactone

Blastmycic acid

The overall degradation of antimycin A$_1$ in buffer systems appears to follow consecutive first order kinetics (Hussain, 1969).

pH	k_1 min^{-1}	k_2 min^{-1}	pH	k_1 min^{-1}	k_2 min^{-1}
7.55	0.00025	-----	11.1	0.6	0.16
8.65	.0029	-----	11.25	1.1	----
9.0	.0052	-----	11.3	---	0.2
10.0	.06	0.015	11.4	---	0.39
10.21	.098	-----	11.85	---	1.1
10.45	----	0.045			

AROCLOR   (PCB, Clophen)   [Polychlorinated Biphenyl]

Mono-, di-, tetra-, and hexachloro-biphenyl isomers were administered
to young male rats, pigeons, and brook trout. No hydroxylated prod-
ucts were produced by brook trout. When the 4-chlorobiphenyl was
administered, in the excreta of pigeons, only the monohydroxylated
derivative was observed and in rodent urine and feces mono- and di-
hydroxychlorobiphenyl derivatives were found. When 4,4'-dichloro-
or 2,2',5,5'-tetrachloro-biphenyl was used, only the respective
monohydroxylated derivatives were observed. No hydroxy metabolites
were detected when the hexachlorobiphenyl was used (Hutzinger et al.,
1972).

In other studies, when Aroclor 1254 was fed to male rats, those
components with the shortest retention times showed the greatest
changes when liver residues were chromatographed (Grant et al.,
1971).

Aroclor 1254 was irradicated in hexane, water and benzene. Products
were not identified; but the increase in size of some peaks indicated
an increase in PCB's with lower molecular weights and shorter reten-
tion times (Herring et al., 1972).

UV irradiation of hexachlorobiphenyls in n-hexane, acetone, methanol,
or methanol-water produced photolytic products which had lost one
to six chlorine atoms (Safe and Hutzinger, 1971; Hustert and Korte,
1972).

Photolysis of 3,4,3,4'-tetrachlorobiphenyl produced two compounds
with retention times corresponding to 4,4'-dichloro- and 3,4,3'-
trichloro-biphenyl. From 4,4'-dichlorobiphenyl, photolysis produced
4-chlorobiphenyl (Ruzo et al., 1972).

When thin films of Aroclors were photolyzed in the presence of water,
the major products were those resulting from dechlorination and/or
polymerization. Polar compounds having little or no chlorine were
also produced. 4,4'-di-, 2,2',5,5'-tetra-, 3,3',4,4'-tetra-,
2,2', 4,4',5,5'-hexa-, 2,2',3,3',4,4',5,5'-octa- and decachloro-
biphenyls were studied (Hutzinger et al., 1972).

ARSENICALS

INORGANIC ARSENIC

Microorganisms in sediments that contain arsenic convert arsenic
into dimethyl arsine. A variety of arsenicals are converted into
dimethyl arsine by methanobacteria. Methyl cobalamine serves as
the methyl donor. Pentavalent arsenic is reduced to trivalent
arsenic. This is methylated to form methyl arsonic acid which
is further reduced and methylated to form dimethyl arsinic acid.
Further reduction occurs to form dimethyl arsine (McBide and
Wolfe, 1971).

Cultures from Sargasso Sea water were obtained and incubated with
arsenite and arsenate. When the bacterial population entered log
phase growth, arsenate began to be replaced by arsenite (Johnson,
1972).

ORGANOARSENIC

CACODYLIC ACID   (Ansar 138)   [Dimethylarsinic Acid]

^{14}C-Cacodylic acid was added to soils. Under anaerobic conditions,
about 61% of the cacodylic acid was converted to a volatile organo-
arsenical within 24 weeks. Under aerobic conditions, only 35% was
converted to volatile organo-arsenical material. About 41% was
converted to $^{14}CO_2$ and arsenate within 24 weeks also (Woolson and
Kearney, 1973).

Loss of arsenic from soil treated with cacodylic acid (dimethyl
arsinic acid) was a function of soil type. The pungent garlic odor
detected suggested the production of a volatile alkyl arsine
(Kearney and Woolson, 1971a).

Microbial cultures metabolized cacodylic acid by oxidative cleavage
of the carbon-arsenic bond and by reduction to an alkyl arsine.
The oxidative pathway produced As^{+5}. Reductive metabolism by
Scopulariopsis brevicaulis produced a pungent volatile material
believed to be dimethyl arsine (Kearney and Woolson, 1971b).

MAA [Methylarsonic acid]

MSMA (Ansar 170; Ansar 529)   [Monosodium methylarsonic acid]

DSMA (DMA)   [Disodium methylarsonic acid]

In johnsongrass (Sorghum halepense L.), methanearsonic acid was
taken up and complexed. Analyses indicated conjugates with
sugar(s), amino acid(s), and organic acid(s). There were indica-
tions that at least one amino acid was a histidine analog (Sckerl
and Frans, 1969).

MSMA was converted in part in bean plants (Phaseolus vulgaris L.)
to a ninhydrin-positive complex (Sachs and Michael, 1971).

Using C^{14} labeled DSMA, studies showed that DSMA was readily taken
up by Bermudagrass from nutrient solution but only slowly from soil.
After foliar treatment, about 25% was translocated to roots and
rhizomes within five days. Only a small amount of $C^{14}O_2$ was detected.
Apparently, the C-As bond remained largely intact (Duble et al., 1969).
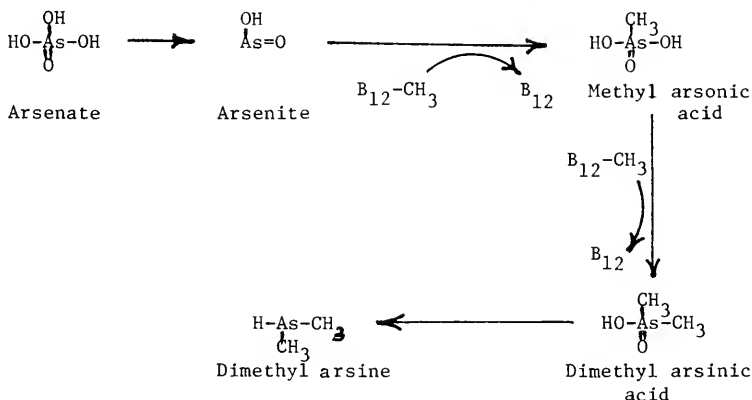
AZIDE

A solution of potassium azide in distilled water will be slightly
alkaline because of hydrolysis.

$$HOH + KN_3 \rightleftarrows HN_3 + K^+ + OH^-$$
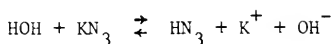
Thus, with clay two possible reactions can be projected.

$$Clay -H + KN_3 \rightleftarrows Clay -K + HN_3$$

or

$$Clay -Ca + 2KN_3 \rightleftarrows 2 Clay K + Ca(N_3)_2$$
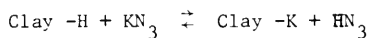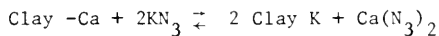
It would appear, therefore, that the biological activity of azide
appears to arise from formation of hydrazoic acid (Parochetti &
Warren, 1970).

<u>AZINPHOSMETHYL</u>   (Methylguthion)   [0,0-Dimethyl S-(4-oxo-1,2,3-
                   benzotriazin-3-(4H)-ylmethyl phosphorodithioate)]

The metabolism of azinophosmethyl by two hepatic systems was
studied. Both the oxidative and demethylating systems were active.
The rate of disappearance was greater in the demethylating system
than in the oxidative system for all species except the rat.
The rate of the oxidative system derived from female chicken
liver homogenate was significantly lower than that for the male
chicken liver homogenate. This was not noted with the demethy-
lating system. The major metabolite was shown by chromatography
to be the oxon analog (Rao and McKinley, 1969).

With subcellular mouse liver fractions, degradative activity was
associated primarily with microsomal and soluble fractions which
required NADPH. The activity was inhibited by CO. The system
catalyzed hydrolysis, with formation of dimethyl phosphorothioate
and dimethyl phosphate, and removal of azinphosmethyl sulfur to
form the oxygen analog. Dialysis of the soluble fraction destroyed
the degradative activity which could be restored by addition of
glutathione. The enzyme system catalyzed conjugation of glutathione
with azinphosmethyl and the formation of S-methyl glutathione and
desmethyl azinphosmethyl (Motoyama and Dauterman, 1972a).

Both <u>in vivo</u> and <u>in vitro</u>, in the predaceous mite <u>Neoseiulus</u>
(<u>Typhlodromus</u>) <u>fallacis</u>, more azinphosmethyl was metabolized by
a resistant strain than by a susceptible strain. <u>In vitro</u>,
glutathione was required as a cofactor. The major metabolite
was identified as the desmethyl analog. The oxygen analog was
also observed (Motoyama et al., 1971).

Azinphosmethyl degradation in both susceptible and resistant
houseflies (<u>Musca domestica</u> L.) was associated with microsomal
and soluble fractions. The latter required glutathione. The
mixed function oxidases appeared to be important in oxidative
desulfuration and de-arylation. Glutathione transferase, found
in the soluble fraction, catalyzed removal of a methyl group
with formation of methyl glutathione. The oxygen analog of
azinphosmethyl was also de-methylated. No evidence was obtained
for the transfer of benzazimide to glutathione (Motoyama and
Dauterman, 1972b).

Azinphosmethyl did not degrade in water in the dark but proceeded rapidly in UV light (2537A). Very little degradation occurred when yellow (5889A) or red (6563A) light was used. With 2 dimension TLC, autoradiography, and chemical tests, four chloroform soluble products of UV irradiation were identified as benzazimide, N-methyl benzazimide, anthranilic acid, and methyl benzazimide sulfide (or disulfide). Water soluble products were not identified. The insecticide was stable at pH 6 to 9; gave 18% water-soluble products at pH 10; and at pH 11, 97% of applied azinphosmethyl was converted to radioactive water-soluble materials (Liang and Lichtenstein, 1972).

Soils were treated with azinphosmethyl granules. One year later, 13% of the applied dosage was recovered as azinphosmethyl, mercaptomethyl benzazimide, N-methyl benzazimide, N-methyl benzazimide sulfide or disulfide, benzazimide, and four unidentified compounds (Schulz et al., 1970).

<u>AZODRIN</u> (Monocrotophos, <u>N</u>-methyl bidrin) [3-hydroxy-<u>N</u>-methylcrotonamide dimethyl phosphate]

The breakdown of azodrin after foliar application to maize, cabbage, apples, cotton and corn was studied. Degradation products were primarily of a hydrophilic nature. On maize, residues of the amide(VI) were found on only one sample. Residues of hydrophilic compounds included the alcohol (IX) and acids such as compound (II) and probably dimethyl phosphate. The <u>N</u>-hydroxymethyl (IV) and its conjugate were also observed. On apples, the main compounds were hydrophilic compounds that included the alcohol (IX), a neutral conjugate and acids such as the <u>O</u>-desmethyl compound (II) and dimethyl phosphate. A conjugate of the <u>N</u>-hydroxymethyl (IV) with a sugar other than β-D-glucose was observed. Compounds III and VI were also found. On cabbage, compounds II and IX, an unidentifed conjugate, and dimethyl phosphate were present. On cotton, the alcohol (IX), <u>O</u>-desmethyl compound (II), a conjugate and some polar compounds were observed (Beynon and Wright, 1972).

Two plots of mature Valencia orange trees were sprayed with Azodrin. One at the rate of 10 lbs. and the other 1 lb. technical Azodrin per acre. The residue half-life was 16 and 13 days, respectively. Azodrin penetrated into the rind rapidly and was not removed by washing the fruit 12 days after treatment. During preparation of the rinds for cattle feed, Azodrin residues were reduced to non-detectable levels (Westlake et al., 1970).
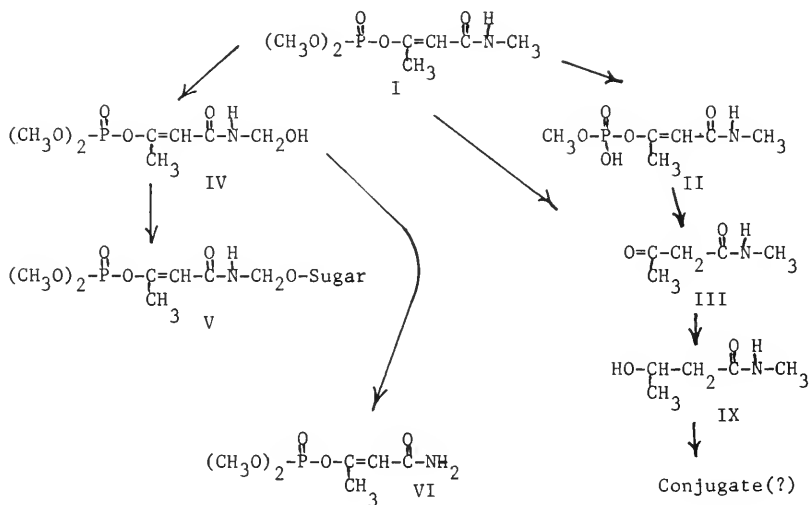
<u>BANOL</u> [2-Chloro-4,5-dimethylphenyl-<u>N</u>-methylcarbamate]

Human embryonic lung cells in monolayer culture metabolized more than 90% of labeled banol within 3 days. The data indicated glucuronic acid conjugation with the phenol (Locke et al., 1971).

When banol was incubated with human and rat liver preparations, the <u>N</u>-hydroxymethyl analog was produced. In addition to 2-chloro-4,5-<u>x</u>ylenol, several additional compounds have been tentatively identified as the carboxyl analogs of banol and its phenol moiety (Strother, 1972).

Bermuda grass was treated at a rate of 1.12 Kg. active ingredient per hectare. Both banol and 6-chloro-3,4-xylenol were found. After 14 days, residues diminished by two-thirds (Argauer, 1969).

BARBAN (Carbyne) [4-Chloro-2-butynyl N-(3-chlorophenyl carbamate]
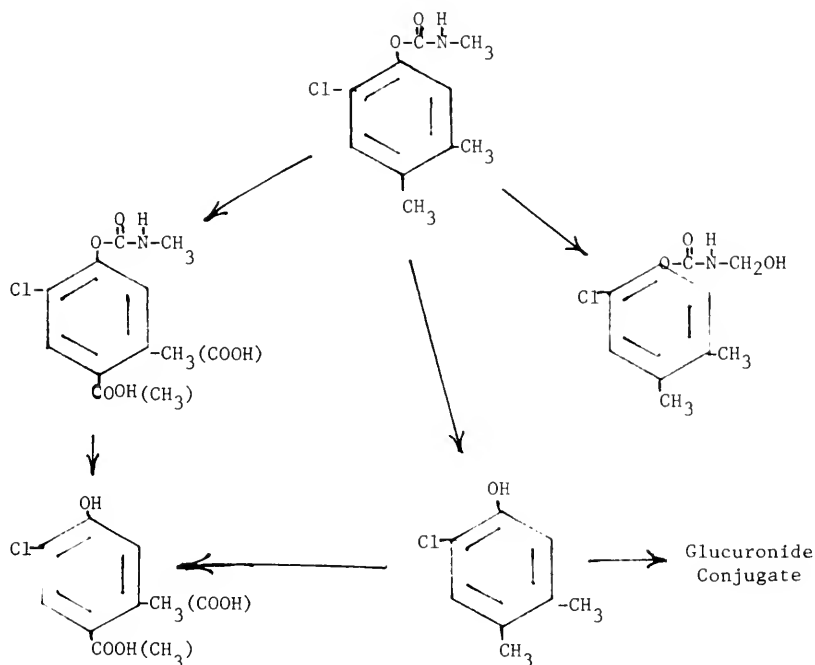
When Barban was orally administered to rats, hydroxylation and
side-chain oxidation occurred. Chloro-aniline, 2-amino-4-
chlorophenol and 4-amino-2-chlorophenol were excreted free and
in conjugated form. Side-chain oxidation was only of minor
importance in the metabolism of barban (Grunow et al., 1970).
In addition to aniline and m-chloroaniline, the hydroxycarbamate
was found in blood and all organs. Urine contained p-aminophenol
(Aleksandrova and Klisenko, 1971).

Soybean plants, root fed with barban, converted barban to polar
metabolites which yielded 3-chloroaniline after alkaline hydrolysis
(Still and Mansager, 1971 and 1972).
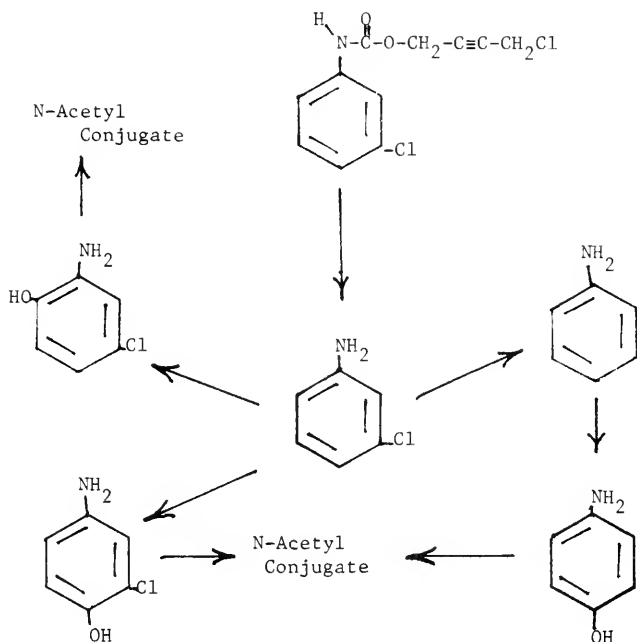
<u>BAS-305</u> [2-Methylbenzanilide]

<u>BAS-307</u> [2-Chlorobenzanilide]

Incubation of BAS-305 or BAS-307 with the fungus <u>Rhizopus Japonicus</u> yielded the corresponding p-hydroxyanilino analogs (Wallnofer et al., 1971).
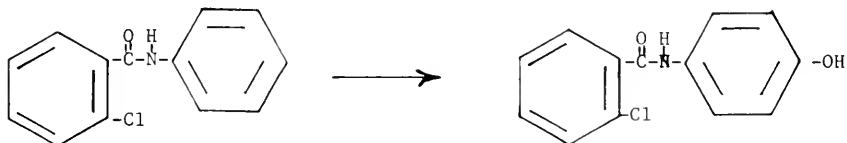
When Bas 3191 was added to cultures of fungi (Rhizopus japonicus, Rhizopus nigricans, Rhizopus peka, and two strains of Mucor), the fungicide was metabolized to the two isomeric N-hydroxymethyl analogs. Identification was made with NMR and mass spectrometric analyses (Wallnofer et al., 1972).

BAYER 9017 [O,O-diethyl O-(4-methylthio-3,5-xylyl)phosphorothioate]
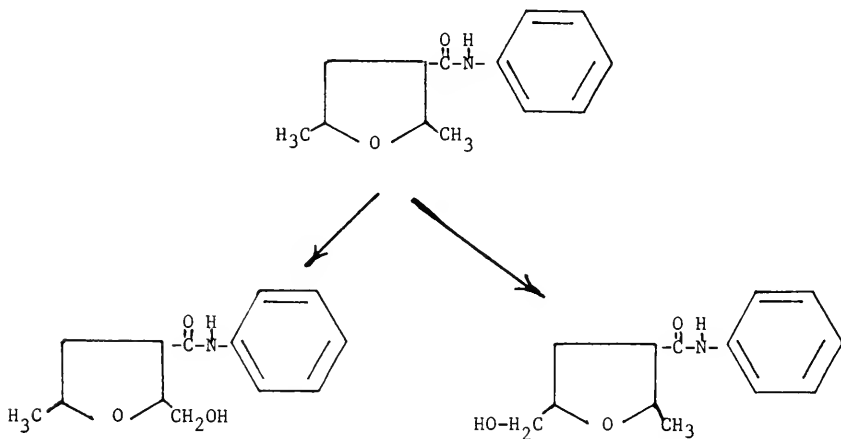
Labeled Bayer 9017 was administered orally to one calf and dermally to another calf. Peak concentration occurred in the blood 12 hours later following both treatments. Urine and tissue contained 8 identified metabolites: the sulfoxide and sulfone of Bayer 9017; the oxygen analog and its sulfoxide and sulfone; the hydrolysis product xylenol and its sulfoxide and sulfone (Young et al., 1969).
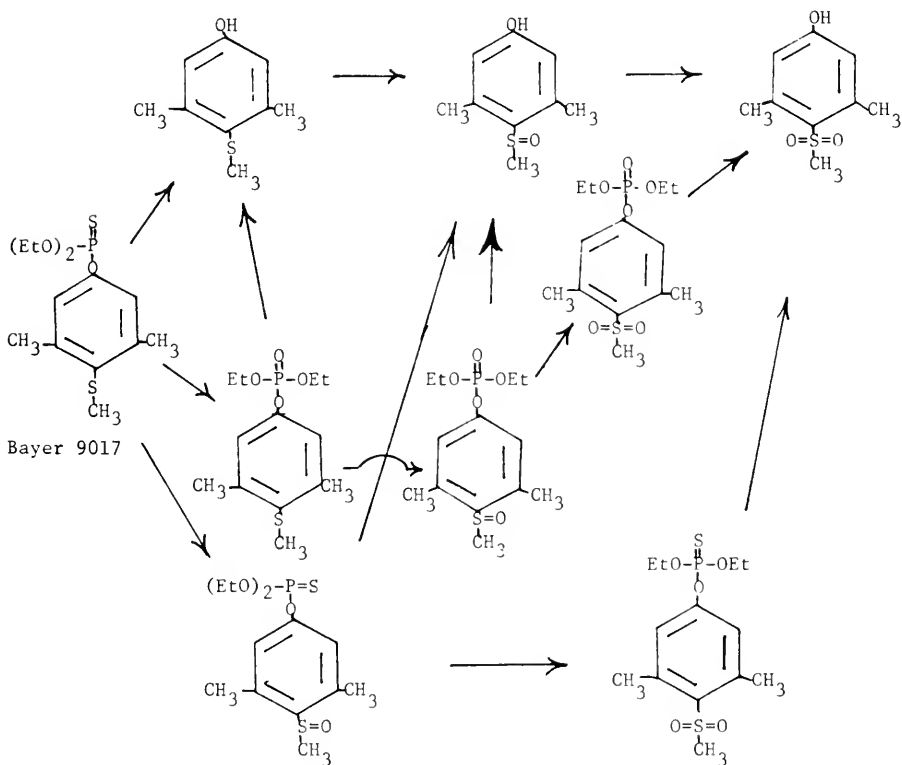
BAYER 93820   [Isopropyl salicylate O-ester with O-methyl phosphoramido-
              thioate]

In cotton plants, Bayer 93820 was metabolized to the oxygen
analog and about three unidentified compounds (Bull and Whitten,
1972).

$$
\begin{array}{c}
\text{CH}_3 \\
\text{O} \quad \text{O-CH-CH}_3 \\
\backslash\text{C} \\
\end{array}
\qquad
\begin{array}{c}
\text{NH}_2 \\
\text{O-P=S} \\
\text{OCH}_3
\end{array}
$$

$$
\downarrow
$$

$$
\begin{array}{c}
\text{CH}_3 \\
\text{O} \quad \text{O-CH-CH}_3 \\
\backslash\text{C} \\
\end{array}
\qquad
\begin{array}{c}
\text{NH}_2 \\
\text{O-P=O} \\
\text{OCH}_3
\end{array}
$$
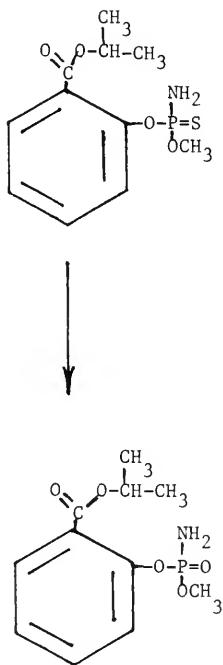
BENEFIN [α,α,α-Trifluro-2,6-dinitro-N-n-butyl-N-ethyl-p-toluidine]

When soil treated with Benefin was flooded with water, Benefin
decomposed rapidly. Only 4.6% was detectable after 16 days.
The major degradation products were benefin with one nitro group
reduced; with both nitro groups reduced; and with both nitro
groups reduced plus removal of both alkyl groups. Five other
metabolites were detected by GLC and TLC in conjunction with
radiochemical methods. These compounds (VII, VIII, IX, X, XI)
constituted less than 5% of the total radioactivity. Extractable
polar products were observed and believed to be aromatic amine
condensation products.

Under aerobic conditions, Benefin degradation in soil was slower.
Degradation products detected included compounds II, IV, V, VI,
VII, VIII, IX, X, XI and XIII.

The degradation products found in plant tissues of peanuts and
alfalfa grown in treated soil reflected those products found in
soil. Compounds VII, XII, and VI appeared in highest concentrations
(9 to 39 ppb, 2 to 57 ppb, and 8 to 33 ppb, respectively). The
other compounds appeared in amounts of less than 2 ppb.

After 12 hour incubation of benefin in artificial rumen fluid,
99.9% of the benefin had been degraded. The major products were
compounds II, IV and VI. Compounds VII, VIII, IX and XI were also
detected in small amounts. Non-identified polar products and
non-extractable radioactive products increased continously.

Following oral administration of benefin to a lactating goat,
almost complete recovery of the administered radioactivity was
obtained in urine (10.8%) and feces (89.1%) within 5 days. The
nature of the radioactivity was not determined. However, because
of the similarity of degradation of benefin to that of trifluralin
in other systems, it was assumed that the excretory products
following benefin ingestion would be analogous to those found with
trifluralin (Golab et al., 1970).

O_2N $\overset{H\diagdown C_4H_9}{\diagup}$ NO_2 CF_3 (VIII)

$C_4H_9\diagdown N\diagup CH_2-CH_3$ O_2N NO_2 CF_3 (I)

$C_4H_9\diagdown N\diagup C_2H_5$ O_2N NH_2 CF_3 (II)

O_2N $\overset{H\diagdown C_2H_5}{N}$ NO_2 CF_3 (IX)

O_2N $\overset{H\diagdown C_2H_5}{N}$ NO_2 CF_3 (XIII)

$C_4H_9\diagdown N\diagup C_2H_5$ NH_2 NH_2 CF_3 (IV)

O_2N $\overset{C_4H_9\diagdown H}{N}$ NH_2 CF_3 (X)

H_2N NH_2 CF_3 (VI)

O_2N $\overset{NH_2}{}$ NO_2 CF_3 (V)

H_2N $\overset{C_4H_9\diagdown H}{N}$ NH_2 CF_3 (XI)

O_2N OH NO_2 CF_3 (XII)

O_2N NH_2 NH_2 CF_3 (VII)

50
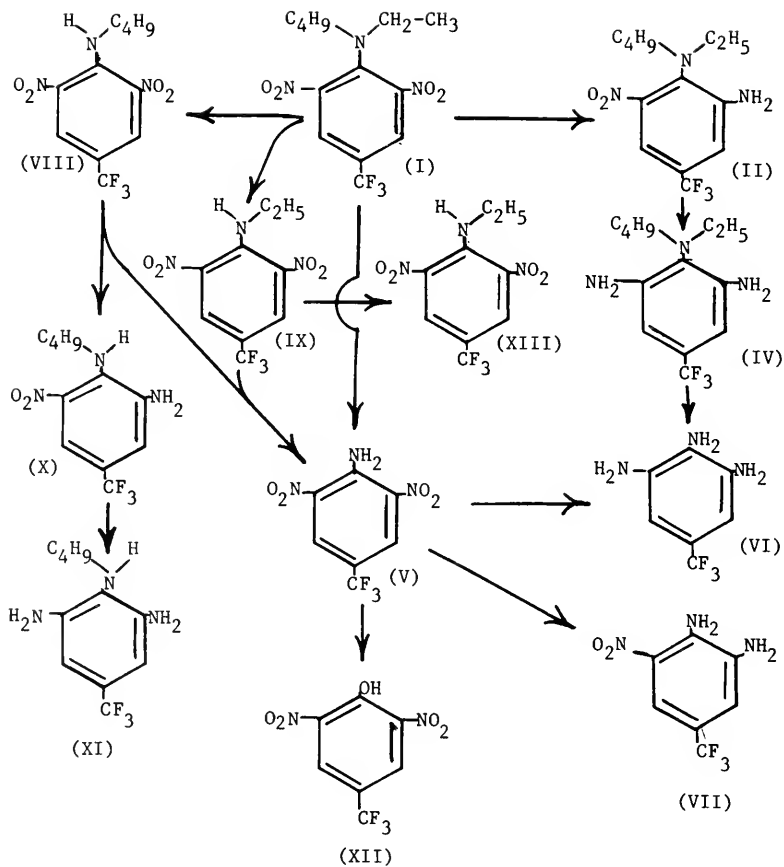
BENOMYL (Benlate, Dupont F-1991) [Methyl N-(N-Butylcarbamoyl-2-
         benzimidazolyl carbamate]

MBC [Methyl N-(2-benzimidazolyl) carbamate]

THIOPHANATE [1,2-Bis(3-ethoxycarbonylthioureido) benzene]

THIOPHANATE-METHYL [1,2-Bis(3-methoxycarbonylthioureido) benzene]

MCA [2-(3-Methoxycarbonylthioureido) aniline]

Cotton seedlings were drenched weekly with Benomyl for 3 weeks and
then assayed. A compound was isolated and characterized as
N-(2-benzimidazole) methyl carbamate (Sims et al., 1969). The same
metabolite has been identified in other studies (Kilgore and White,
1970).

Numerous studies have indicated that the thiophanates were converted
to benzimidazol-2-ylcarbamates which were responsible for the
fungitoxic effects. When orally administered to rats, thiophanate-
methyl was rapidly excreted via urine, feces and as CO_2. In rats,
the main product was MBC. Smaller amounts of the 5-hydroxy analog
and its glucuronide and three N-glucuronides were also observed.
A minor amount of desulfuration also occurred (Noguchi, 1971).

On apple and grape leaves, thiophanate-methyl half-life was about
two weeks under natural summer conditions. The major metabolite
was identified as compound III and a minor product as compound IX
(Noguchi, 1971 and 1972; Soeda et al., 1972b).

After application of thiophanate-methyl to bean leaves, a number
of compounds were detected. Some were metabolites and others
were non-biological degradation compounds. The major metabolite
was compound III. The ethyl analog behaved similarly (Soeda et al.,
1972a).

In soil thiophanate-methyl decreased to less than half the initial
dose within 2 days after application. Within 7 days it almost
completely disappeared. The fungicide is transformed into MBC at
a moderate rate (Noguchi, 1971).

Suspensions of <u>Cladosporium</u> <u>cucumerinum</u> converted Benomyl, thiophanates, and MCA into MBC (Vonk and Sijpesteijn, 1971).

In aqueous solution, benomyl, methyl thiophanate, and thiophanate decompose to MBC and the ethyl analog, respectively (Clemons and Sisler, 1969; Peterson and Edgington, 1969; Selling et al., 1970).

$C_4H_9NH_2$

+

CO_2

$\longleftarrow$ [$C_4H_9\overset{H}{N}-\overset{O}{C}-OH$] $\longleftarrow$

Benomyl (I)

$\overset{N}{\underset{N}{\bigcirc}}$ $C-\overset{H}{N}-\overset{O}{C}-OCH_3$

$O=C-\overset{}{N}-C_4H_9$
H

(II)

Animal $\downarrow$ Plant

(IX)

Animal
Plant
Soil

(X)

$HO-$ $C-\overset{H}{N}-\overset{O}{C}-OCH_3$ (IV)

MBC (III)

Animal

Animal

Animal

Animal

(VI)

(V)

(VII)

(VIII)

Glucuronide

Gluronide

53
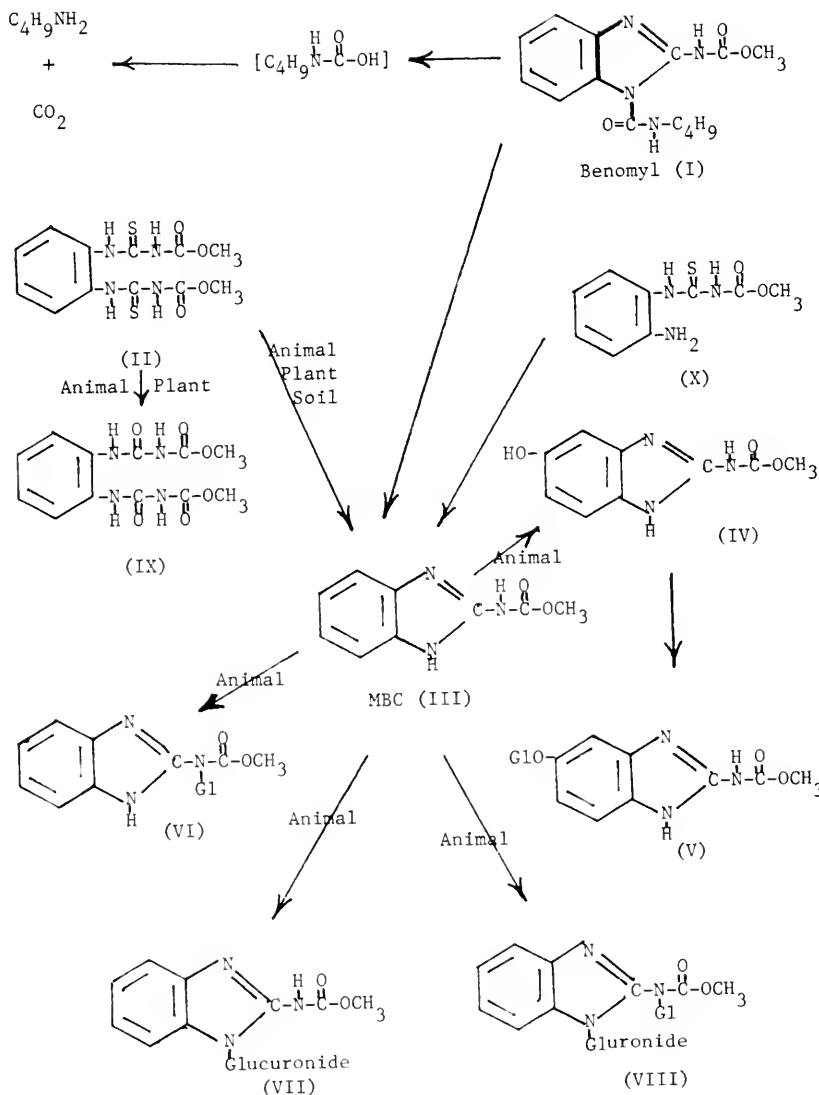
BHC [1,2,3,4,5,6-Hexachlorocyclohexane]

Lindane = γ-BHC

Rabbits metabolized lindane to o-dichlorobenzene, 1,2,4-trichloro-
benzene, 1,2,3,4-, 1,2,3,5- and 1,2,4,5-tetrachlorobenzene,
pentachlorobenzene, 2,3-, 2,4-, and 2,5-dichlorophenol, 2,3,5-,
2,4,5- and 2,4,6-trichlorophenol, 2,3,4,5-, 2,3,4,6-tetrachlorophenol
and pentachlorophenol (Karapally et al., 1971).

Rats receiving lindane in their diet excreted compounds identified
as 3,4-dichlorophenol; 2,3,5-, 2,4,5- and 2,4,6-trichlorophenol;
2,3,4,5- and 2,3,4,6-tetrachlorophenol. In addition 2,3,4,5,6-
pentachlorocyclohex-2-enol was found (Chadwick and Freal, 1972).
After p.o. administration of the β-isomer, 2,4,6-trichlorophenol
was the main excretion product; 2,4,5- and 2,4,6-trichlorophenols,
after feeding the α and δ isomers; and 2,4,5-trichlorophenol after
feeding γ-PCCH (Freal and Chadwick, 1972).

Resistant flies, treated with lindane, formed greater amounts of
1,2,3- and 1,2,4-trichlorobenzene, 1,2,3,4- and 1,2,4,5-tetrachloro-
benzene and iso-pentachlorocyclohexene (iso-PCCH) than did susceptible
flies. The resistant strain produced more 1,2,4-trichlorobenzene
and 1,2,4,5-tetrachlorobenzene after application of γ-PCCH and more
pentachlorobenzene from iso-PCCH. 1,2,3,4-tetrachlorobenzene and
1,2,3-trichlorobenzene were also obtained from the iso-PCCH
(Reed and Forgash, 1968, 1969 and 1970).

After application of ^{14}C-lindane to foliage of cabbage and spinach
and to soil of spinach and carrot seedlings, the presence of five
metabolites was demonstrated by TLC. None were identified
(Itokawa et al., 1970). In other studies with a soil bacterium,
Clostridium sp., an anaerobic metabolite of lindane was observed.
Experiments indicated that the metabolite was neither γ-PCCH nor
one of the 1,3,5- or 1,2,4-trichlorobenzenes. By analogy to the
anaerobic metabolism of DDT, it was speculated that the unknown
metabolite was the product of reductive dechlorination, pentachloro-
cyclohexane (MacRae et al., 1969; Sethunathan et al., 1969).

54

The disappearance of lindane in flooded soil was studied. After mixing 100g soil and 300 ml of water, 1.00 mg lindane in 2 ml acetone was added. The disappearance of lindane and appearance of a metabolite identified as γ-3,4,5,6-tetrachloro-1-cyclohexene (TCCH) were followed. TCCH concentration reached a maximum at 14 days and then decreased. Lindane continued to decrease throughout the study (Tsukano and Kobayashi, 1972).

Volatilization of lindane from soil containing moisture greater than 15 bars tension was dependent on temperature, adsorptive characteristics of the soil, and concentration of the lindane. When soil water approached a monolayer, no more lindane was lost (Guenzi and Beard, 1970). Rapid degradation of lindane was observed under flooded soil conditions. The rate of decomposition was directly related to organic matter levels and temperature. Molecular oxygen, nitrate and manganic oxide retarded the rate of lindane degradation (Yoshida and Castro, 1970).

Algae (Chlorella pyrenoidosa and Chlorella vulgaris) metabolized lindane to 2,3,4,5,6-pentachlorocyclohex-1-ene (Elsner et al., 1972).

R= Glutathione

R'=Sulfates and
Glucuronides
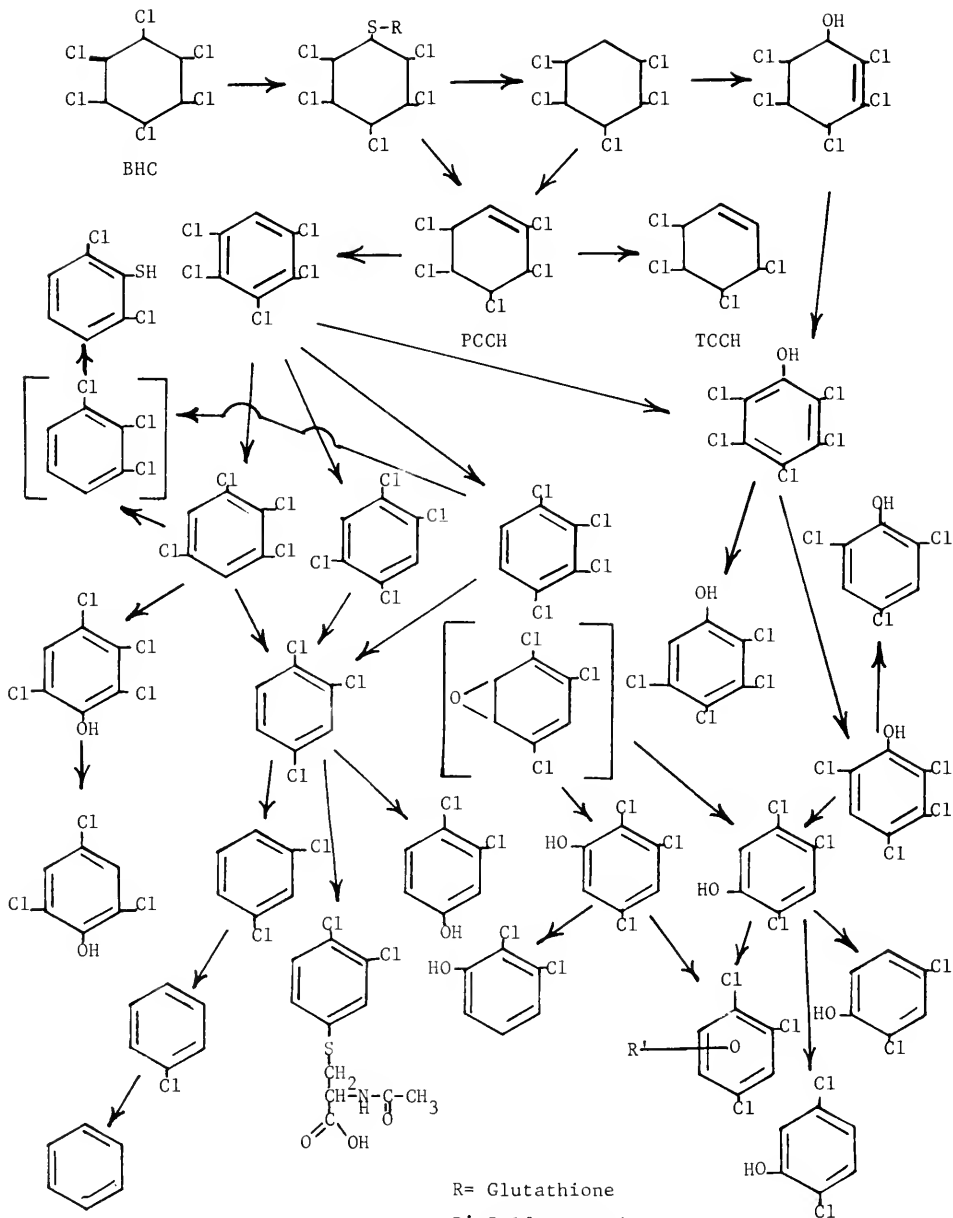
BIOXONE [2-(3,4-dichlorophenyl)-4-methyl-1,2,4-oxadiazolidine-3,5-dione]

Bioxone was readily metabolized by cotton (Gossypium hirsutum L.) to 1-(3,4-dichlorophenyl)-3-methylurea (DCPMU) and 1-(3,4-dichlorophenyl)urea (DCPU). Three days after treatment of excised leaves, DCPU accounted for 55-70% of applied ^{14}C. Intact roots metabolized Bioxone rapidly to DCPMU and DCPU. Little or no intact herbicide was translocated from roots to leaves but radioactivity in the leaves accounted for 80-90% of methanol-soluble label at 47 days posttreatment. Most of this ^{14}C was recovered as DCPU (50-60%) and unidentified polar metabolite(s) (30-40%). Some conjugation of plant proteins with DCPMU and DCPU was indicated in studies of the digestion of plant residues with the proteolytic enzyme pronase.
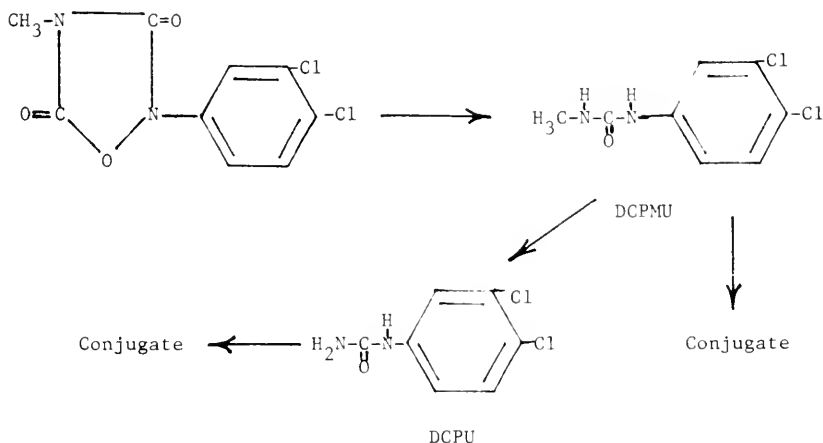
After feeding of biphenyl to rabbits, 2-hydroxy-, 4-hydroxy-, 3,4-dihydroxy-, and 4,4'-dihydroxy-biphenyl were demonstrated. Three other phenolic metabolites were present but not identified (Raig and Ammon, 1970).

In adult male Swiss mice, intraperitoneal injection of piperonyl butoxide produced a transient stimulation of o-hydroxylation and a concomitant suppression of p-hydroxylation of biphenyl by their liver microsomes (Jaffe et al., 1969).

Gram-negative bacteria isolated from soils were capable of utilizing biphenyl as a sole carbon source. 2,3-Dihydroxybiphenyl was isolated from cultures after incubation with biphenyl. A particulate fraction from biphenyl-grown cells cleaved the dihydroxybiphenyl to give α-hydroxy-β-phenylmuconic semialdehyde. This was converted to phenylpyruvate, through unknown intermediates, by a soluble cell-free extract (Lunt and Evans, 1970).
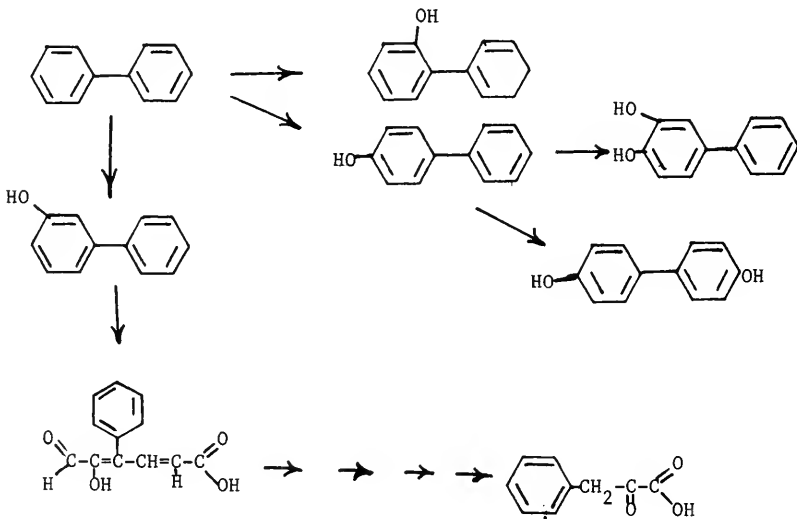
Bis(chloromethyl)sulfone

After administration to sheep and cattle. bis(chloromethyl)sulfone was metabolized. CO_2 was found in exhaled air. Chloromethanesulfinic acid and chloromethanesulfonic acid were found in urine. Liver and kidney tissues contained carboxyl labeling; and radioactive uric acid, urea, and amino acids were observed in urine (Wolfe et al., 1972).

$$Cl-CH_2-\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}-CH_2-Cl \xrightarrow{O_2} Cl-CH_2-SO_2H \quad + \quad CO_2 \quad + \quad HCl$$

$$Cl-CH_2-SO_3H$$

Amino acids,

Uric acid,

Urea
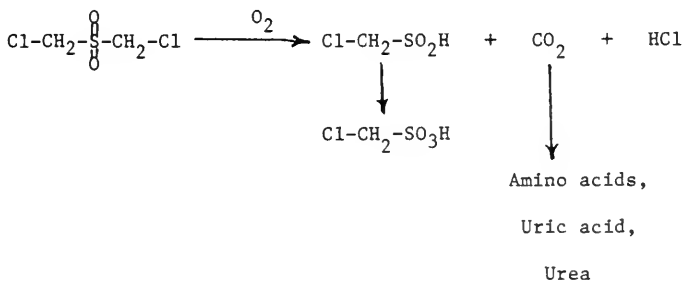
BLASTICIDIN S   [N-[6-(4-Amino-1,2-dihydro-2-oxo-1,3-diazin-1-yl)-
                2-carboxy (2H, 3H, 6H)pyran-3-yl]-3-amino-5-
                (1-methylguanidino)pentamide]

After application to rice plants via culture solution, Blasticidin S
was degraded. A small amount of cytomycin and deaminohydroxyblasticidin S
were observed. When incubated with microorganisms, Blasticidin S was also
degraded: soil bacterium (unidentified) >Ps. aeruginosa > Phytophythora
parasitica > Fusarium oxysporum > soil fungus (unidentified) > Ps. ovalis
1002 > Ps. marginalis. After exposure to washed mycelia of a soil fungus,
the main products of degradation were identified as deaminohydroxy-
blasticidin S, cytomycin, and deaminohydroxycytomycin (Yamaguchi
et al., 1972).
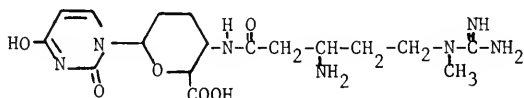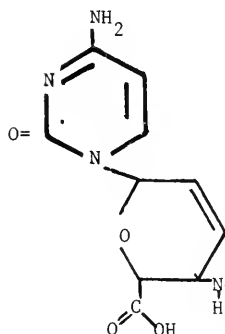
Deaminohydroxyblasticidin S

Deaminohydroxycytomycin

Blasticidin S
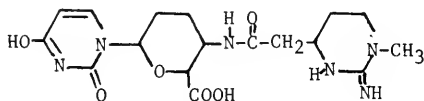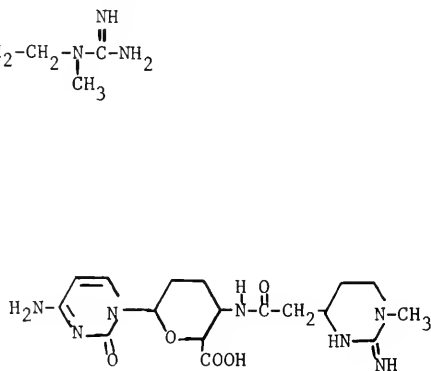
Cytomycin

BOH [2-Hydroxyethylhydrazine]

When BOH was added to aqueous solutions of ferrous sulfate or cuprous oxide, ethylene was produced. Maximum yield was 16% from the cuprous system and 4% from the ferrous system (Dollwet and Kumamoto, 1972).

BROMOPHOS [O-(4-Bromo-2,5-dichlorophenyl)-O,O-dimethyl phosphorothioate]

Following oral administration of bromophos to pregnant albino rats, traces of bromoxon were detected in muscle tissue of the fetus (Ackermann and Engst, 1970).

Incubation of bromophos with a glutathione-dependant liver enzyme gave rise to bisdesmethyl bromophos (Steversen, 1969). Similarly, after cutaneous application of bromophos to a lactating cow, only the bisdesmethyl bromophos was observed (Dedek & Schwarz, 1969).

When tomato plants were exposed to Bromophos, it penetrated from the leaf surface to the interior and from a nutrient solution into the root but did not act systemically. In addition to unchanged bromophos, dichlorophenol (the main metabolite), bromoxon, monodesmethylbromophos, dimethyl phosphorothioate, and inorganic phosphate were recovered (Stiasni et al., 1969).

Seeds of onion, carrot and wheat were treated with labeled bromophos. Wheat was most active and carrot least active in metabolizing the bromophos. The main metabolites were inorganic phosphates and other compounds with $R_f=0$. Desmethyl bromophos was located mainly in the leaves (Stenersen, 1969).

After incubation of the fungi Alternaria tenius and Trichoderma lignorum with bromophos, dimethyl and methyl phosphorothioate, bisdesmethylbromophos, and desmethylbromophos were observed (Stenersen, 1969).

The beetle Tribolium castaneum was treated topically with bromophos. The main hydrolysis product was O-demthylbromophos. Dimethyl thiophosphate and a little dimethyl phosphate were also found. Some phenol and small amounts of the oxon were observed (Dyte and Rowlands, 1970).

$HO-\overset{\overset{\displaystyle S}{\|}}{\underset{\displaystyle O}{P}}-OCH_3$

Cl, Cl, Br

$CH_3O-\overset{\overset{\displaystyle S}{\|}}{\underset{\displaystyle O}{P}}-OCH_3$

Cl, Cl, Br

Bromophos

$HO-\overset{\overset{\displaystyle S}{\|}}{\underset{\displaystyle O}{P}}-OH$

Cl, Cl, Br

$(CH_3O)_2-\overset{\overset{\displaystyle OH}{|}}{P}=S$

OH, Cl, Cl, Br

$CH_3O-\overset{\overset{\displaystyle O}{\|}}{\underset{\displaystyle O}{P}}-OCH_3$

Cl, Cl, Br

Bromoxon

$CH_3O-\overset{\overset{\displaystyle OH}{|}}{\underset{\displaystyle OH}{P}}=S$

$HO-\overset{\overset{\displaystyle OH}{|}}{\underset{\displaystyle OH}{P}}=S$

$(CH_3O)_2-\overset{\overset{\displaystyle OH}{|}}{P}=O$

$CH_3O-\overset{\overset{\displaystyle OH}{|}}{\underset{\displaystyle OH}{P}}=O$

Inorganic Phosphate

Radioautographic analyses, after application of ^{14}C-bromoxynil
to leaves of wheat and coast fiddleneck, showed that most of
the label remained in the leaves. The amount of ^{14}C-bromoxynil
unabsorbed was greater in wheat than in coast fiddleneck. Soluble
activity recovered from coast fiddleneck was greater than from
wheat. The activity was also more uniformly distributed in the
former. In both plants, most of the soluble lable was present
as bromoxynil. Four other labeled compounds were present in
small amounts but were not identified. [14]CO$_2$ was also formed.
Since decarboxylation gave rise to [14]CO$_2$, the benzamide and
benzoic acid analogs are implicated as intermediates in the
degradation, as well as the probable end product 3,5-dibromo-4-
hydroxybenzene (Schafer and Chilcote, 1970).

Bromoxynil
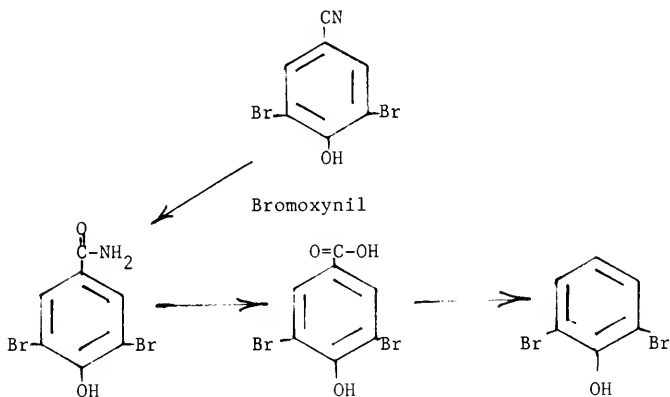
BUSULFAN (Myleran) [1,4-Butanediol dimethanesulfonate]

After injection into rats, Busulfan disappeared rapidly from
the circulation. Appreciable amounts of $1,4-C^{14}$-butane were
recovered as $^{14}CO_2$; small amounts of label were recovered in
urinary glucose, oxalate and urea. ^{35}S-label was recovered
in the urine almost quantitatively as methanesulfonate and
unchanged Busulfan. Only small amounts of inorganic-^{35}S was
found. The major metabolite exhibited characteristics of a
glycol but was not identified (Trams et al., 1959).

About 40% of labeled Busulfan fed to boll weevils (Anthonomus
grandis Boheman). was metabolized to CO_2 . 36% of the radio-
activity appeared in the fross and 8% of the label was in the
weevil (Nelson et al., 1972).

Most of the metabolism of busulfan by the boll weevil(Anthonomus
grandis Boheman) occurred within 24 hours of ingestion. Metabolites
included organic acids, amino acids, 1,4- and 2,3-butanediols,
sulfolane and methanesulfonic acid. After feeding of ^3H- and
^{14}C-labeled busulfan to day-old boll weevils, labeling was found
in citric acid, malic and malonic acids, succinic acid, fumaric
acid, α-ketoglutaric acid, amines, aldehydes, amino acids and
CO_2 (Wiygul and Mitlin, 1971).

$$CH_3O-\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}-O-CH_2-CH_2-CH_2-CH_2-O-\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}-OCH_3$$

Busulfan

$HO-CH_2-CH_2-CH_2-CH_2-OH$

+

$CH_3-\underset{OH}{\overset{}{C}}H-\underset{OH}{\overset{}{C}}H-CH_3$

Tricarboxylic
Acid Cycle

Sulfolane

+ CH_3OSO_3H

65
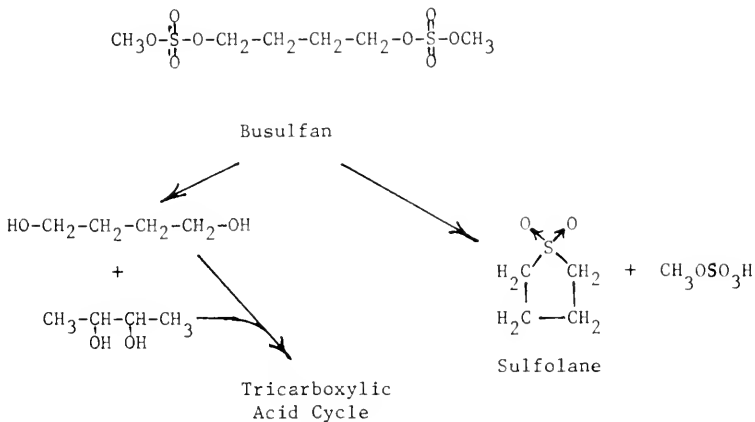
BUTACARB [N-Methyl-3,5-di-tert-butylphenylcarbamate]

When butacarb(I) was incubated with mouse liver 10,000g supernatant, eleven metabolites were detected. Hydrolysis produced only six phenols. One of these, the major metabolite, was identified as 3,5-di-tert-butylphenol. Other metabolites were characterized but not all were completely identified: two acid metabolites containing a carboxyl and carbamoyl group; two containing a carbamoyl and two hydroxy groups (but not dihydroxybenzenoid); a hydroxybutylphenol; one containing a carbamoyl and a hydroxy group; two dihydroxybutylphenols; N-hydroxymethyl butacarb; and the N-hydroxymethyl hydroxybutyl analog.

Studies with the housefly (Musca domestica), the blowfly (Lucilia sericata) and grass grubs (Costelytra zealandica) gave results qualitatively similar to those with mouse liver enzymes (Douch & Smith, 1971a).
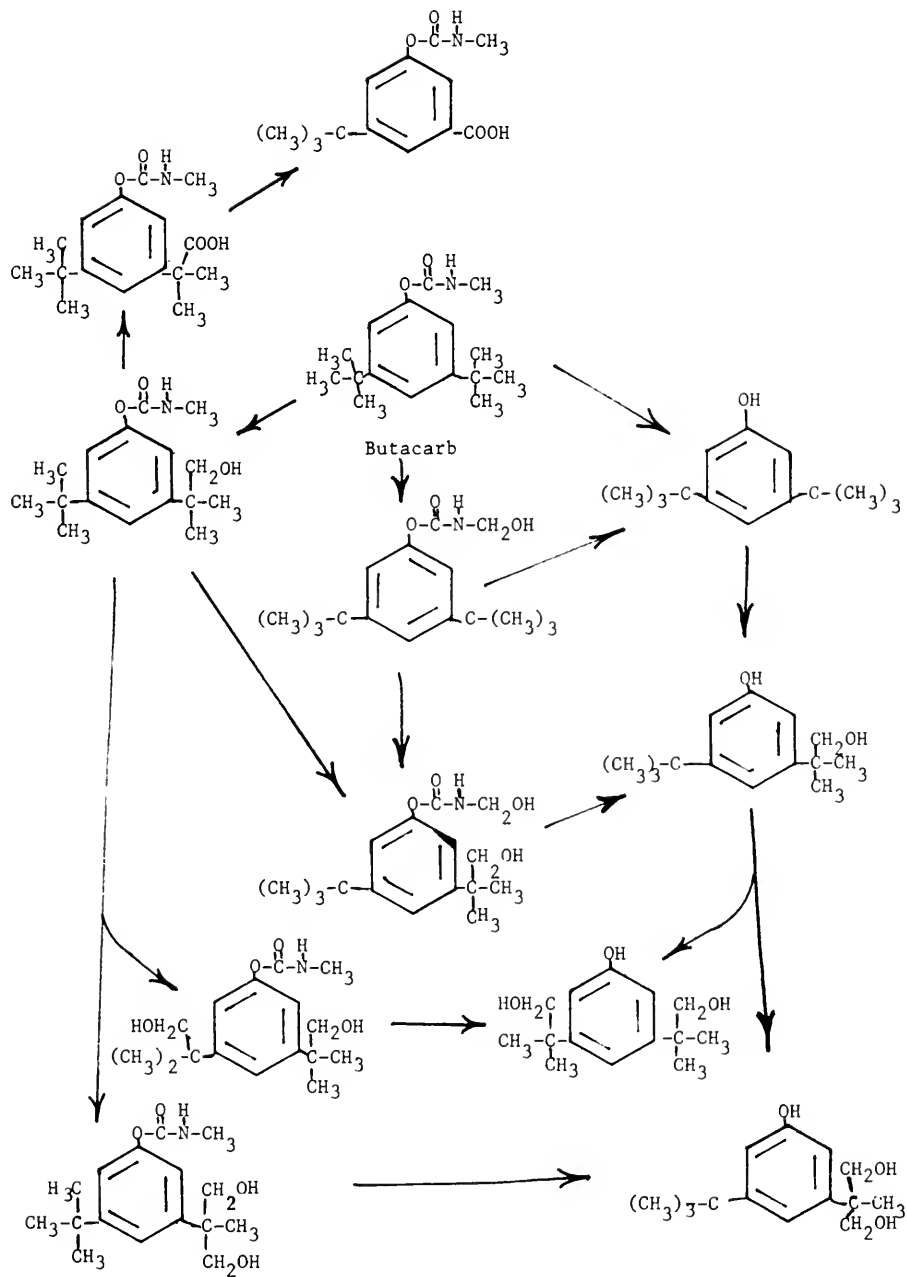
<u>BUX</u> [3:1 mixture of <u>m</u>-(1-methylbutyl)phenyl and <u>m</u>-(1-ethylpropyl) phenyl-<u>N</u>-methylcarbamates]

Both isomers of Bux were metabolized in the same manner in soil. Decreasing amounts of carbonyl labeled Bux paralleled increasing amounts of released $^{14}CO_2$. One ^{14}C-metabolite was observed in the soil and only in trace amounts. This was identified as the 1-hydroxy analog. This metabolite also hydrolyzed to the corresponding phenol (Tucker and Pack, 1972).
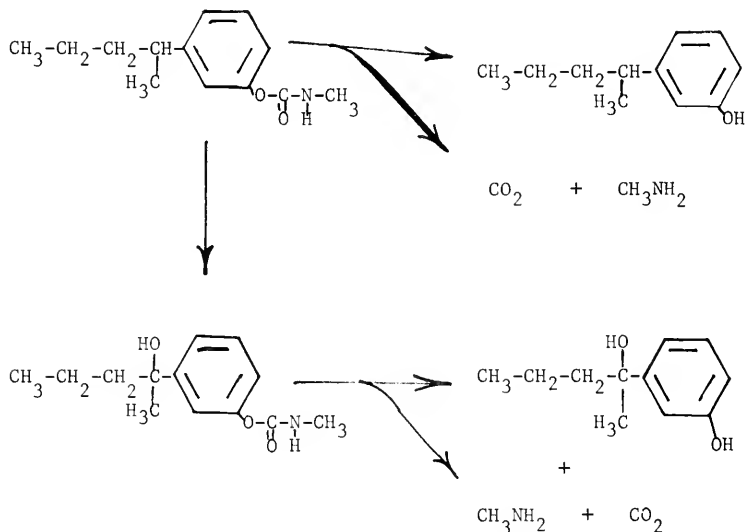
C-8353 [N-Methyl-2-(1,3-dioxolan-2-yl)phenylcarbamate]

Photolysis of C-8353 in methanol yielded a compound assigned the
structure 3-methyl-2H-1,3-benzoxazine-2,4-(3H)-dione. When C-8353
was irradiated in water, 2-(N-methylcarbamoyl)benzaldehyde and
2-(1,3-dioxolan-2-yl)phenol were produced (Pape et al., 1970).
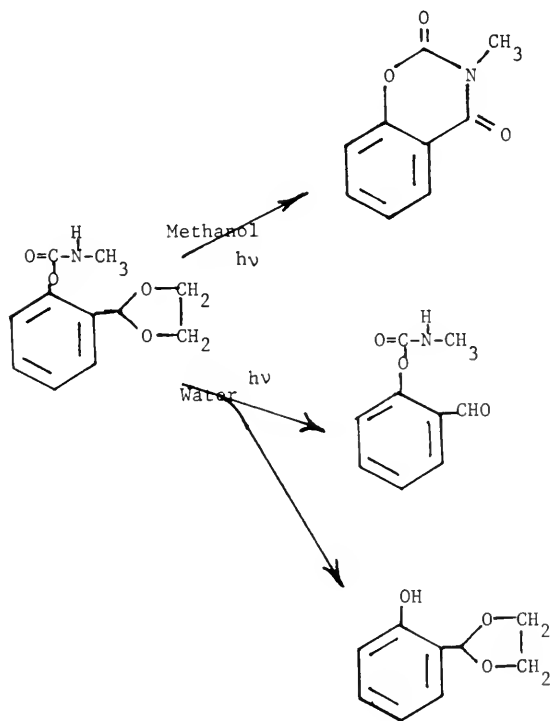
[2,5-dichloro-4-iodophenyl dimethyl phosphorothioate]

When C-9491 was applied to corn at the rate of 2 lbs. per acre, it exhibited a half-life of 3 to 4 days. This decreased to about 1 day at lower rates. The oxygen analog and the phenol were detected. However, after 16 days, no residues of the oxygen analog were observed (Bowman & Young, 1969).

C-9491
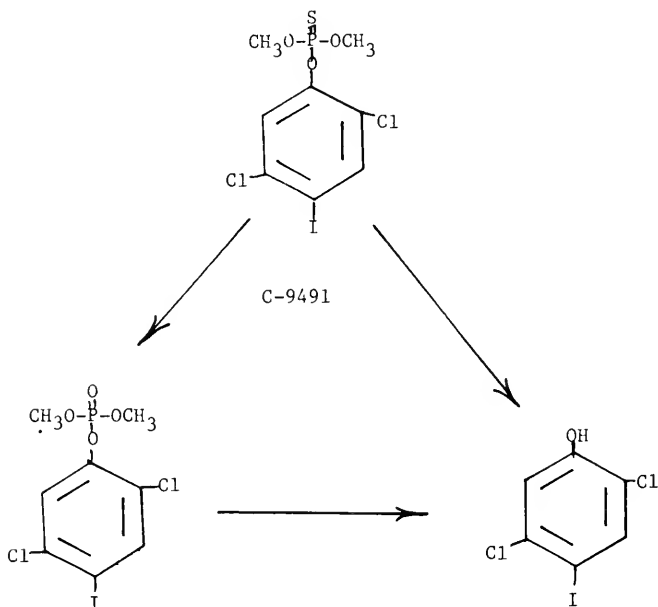
CADMIUM

A low molecular weight (about 10,000) protein metallothionein, found in liver and kidney cortex, showed high affinity for bivalent heavy metals. Cadmium was found to be a permanent component of the native molecule. In human beings exposed to cadmium in industry, the metal accumulated in liver and kidney cortex (Wisniewska-Knypl, et al., 1970 and 1971; Nordberg et al., 1971).

<u>Captax</u> [2-Alkylthiobenzothiazole]

In cotton plants, the defoliant captax was converted to the re-
spective mercaptan plus 1,3-benzothiazole (Imamaliev et al., 1971).
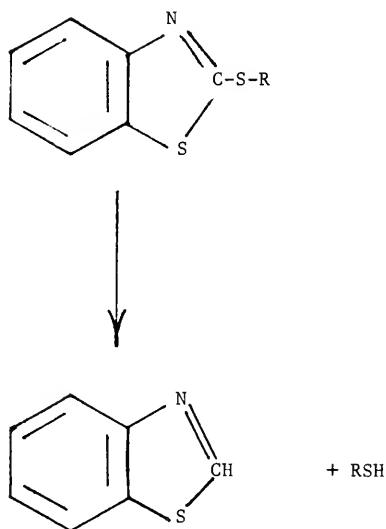
R = Ethyl

= Butyl

=Heptyl

CARBARYL (Sevin) [N-Methyl naphthyl-1-carbamate]

Carbaryl was incubated with human tissues. Hepatic tissue performed
the metabolic processes of demethylation and/or hydrolysis, hydroxyla-
tion, oxidation and conjugation. The kidney produced naphthyl glucuronide;
uterus, lung and placenta produced naphthyl sulfate. Vaginal mucosa
hydrolyzed carbaryl and formed glucuronide and sulfate conjugates (Chin
et al., 1971). Human and rat liver preparations were incubated with
carbaryl. Human liver produced at least 2 unidentified metabolites which
were not observed with rat livers. The N-hydroxy, 4- and 5-hydroxy-
carbaryl analogs were observed (Strother, 1970 and 1972). Hydrolysis
of carbaryl after incubation with human sera varied from one serum to
another. Michaelis constants (K_m), maximal rate of hydrolysis (V) and
the rate constant of spontaneous hydrolysis were determined (Reiner and
Skrinjaric-Spoljar, 1968).

$$K_m = 17 \pm 17 \times 10^4$$

$$V = 17 \pm 11 \times 10^2$$

$$k = 11.5 \quad \times 10^4$$

Radioactive carbaryl, introduced into a culture of human embryonic lung
cells (L-132), was completely metabolized within 3 days to water-soluble
conjugates or organo-extractables. About 40% of the labeled compound
was hydrolyzed to form naphthalene-1,4-diol. The remainder was found
as the N-glucuronides of 4-hydroxycarbaryl and 5,6-dihydroxy-5,6-di-
hydrocarbaryl (Baron and Locke, 1970).

After intraperitoneal administration of labeled carbaryl to rats, urine
and bile were collected and incubated with β-glucuronidase and arylsul-
fatase. Glucuronides and sulfates of 1-naphthol, 4- and 5-hydroxycarbaryl
were observed. Water-soluble metabolites present were identified as
thioether amino acid conjugates. After acid hydrolysis, these conjugates
exhibited chromatographic properties consistent with identification as
S-cysteine conjugates of 4- and 5-hydroxy-1-naphthalene. This would be
consistent with prior formation of a gluthathion conjugate. Similar
results were obtained with supernatant from 10,000 g mouse liver
homogenate preparations (Bend et al., 1971). When small intestines of
male Sprague-Dawley rates were everted and incubated with carbaryl or
1-naphthol, the metabolite 1-naphthyl glucuronide was isolated from
mucosal and serosal fluids (Pekas and Paulson, 1970).

Female rats absorbed labeled carbaryl and expired $^{14}CO_2$ (Casper and
Pekas, 1971).

A single oral dose of carbaryl was administered to rats. After
extraction of collected urine, column and TLC chromatography, ten-
tative identification was made for 1,5-naphthalenediol with small

amounts of carbaryl, 5-hydroxycarbaryl, and a trace of N-hydroxy-
methylcarbaryl was also present. A major metabolite in the urine
identified as 5,6-dihydro-5,6-dihydroxycarbaryl, was found free
(1.4% of the dose) and as the glucuronide (10.5% of the dose).
Naphthyl glucuronide and sulfate was also observed (Sullivan et al.,
1970 and 1972).

Preliminary studies with rat liver cubes, maintained in culture
medium, indicated that about 3% of the metabolites may be N-O-
conjugates of N-hydroxycarbaryl (Locke, 1972).

In the presence of $NADPH_2$, and UDPGA rat liver enzymes metabolized
carbaryl and produced conjugates of 1-naphthol, N-hydroxymethyl-
carbaryl and 5- and 6-hydroxycarbaryl (Mehendale and Dorough, 1971).
Other studies indicated that α-naphthol was metabolized by two micro-
somal systems (Hansen and Hodgson, 1971).

Carbaryl was metabolized by small intestine in vitro to water-soluble
metabolites The primary metabolite was naphthyl glucuronide. In
other studies, carbaryl partially decomposed at pH 7.4 and liberated
free naphthol (Pekas, 1971).

In mucosal fluids of the small intestine, carbaryl was non-enzymatically
hydrolyzed to 1-naphthol and carbamic acid. A similar decomposition
occurred in serosal fluid. In intestine tissue, hydrolysis was enzymatic.
The 1-naphthol produced in fluids and tissue was conjugated as the
glucuronide (Pekas, 1972).

Monoamine oxidase inhibitors adversely affected conjugative mechanisms
most. Oxidative and hydroxylative rates were also reduced (Dorough
et al., 1972).

[14]C-Carbaryl was administered to a cross-bred Holstein cow. Chromatography
of an ether extract of collected urine showed the presence of four com-
ponents. The smaller peaks co-chromatographed with 4-hydroxy- and 5-
hydroxy-carbaryl standards. The third compound gave a positive test for
hydroxymethyl urea after ammonolysis. The largest metabolic component
exhibited an R_f on TLC identical to the metabolite found in milk. The
mass spectral data of the metabolite was consistent with the structure of
a methylcarbamate ester of dihydrodihydroxynaphthol (Baron et al., 1969).

Carbaryl was administered to white Leghorn hens in polyethylene glycol
400 in a gelatine capsule. About 50% of ^{14}C-carbonyl labeled compound
appeared in the respiratory gases during the 48-hour collection period.
Radioactivity from both ring-labeled and carbonyl-labeled carbaryl was
rapidly excreted in the urine during the first 6 hours after the dose
was given. One day after a single dose of ring-labeled carbaryl was
given, ^{14}C appeared in white and yolk of eggs collected (Paulson and
Feil, 1969). Labeled residues were observed in excrement, eggs and
tissues. After discontinuation of dosing, the half-life of labeled
residues was less than one day in excrement and egg white, 2 to 3
days in egg yolk, and 5 days in the carcass. A metabolite tentatively
characterized as 1-naphthyl sulfate accounted for 39% of the residues
in eggs. Other metabolites found in the eggs included: 1-naphthol;

1-naphthyl-N-hydroxymethyl carbamate; 1-naphthol conjugate; 3 unidentified
conjugates; and unchanged carbaryl (Andrawes et al., 1971 and 1972).

In other studies with collected urine, urinary metabolites were identified
as 1-naphthol, 1-napthyl glucuronide, and the sulfate esters of 1-naphthol,
4-hydroxycarbaryl and 5-hydroxycarbaryl. Characterization of hydrolysis
products and acetyl derivatives of the other metabolites indicated that
two were conjugates of 1,5-naphthalenediol, one was conjugated 4-hydroxy-
carbaryl, one was conjugated 5-hydroxycarbaryl, one was conjugated
5,6-dihydroxycarbaryl, one was conjugated 1,5,6-trihydroxynaphthalene,
and two were conjugates of carbaryl (Paulson et al., 1969 and 1970).

During midgut penetration of carbaryl in Mus musculus, Manduca sexta,
and Blaberus discoidalis, 1-naphthol, 4-hydroxy-and N-hydroxymethyl
carbaryl, and an unidentified metabolite were observed (Shah and Guthrie,
1970).

Metabolism of carbaryl was studied in DDT-resistant and parathion-
resistant strains of cabbage looper [Trichoplusia ni (Hubner)] larvae.
In each strain, maximum metabolism occurred in the fat body. The major
metabolite formed in vivo and in vitro was the N-hydroxymethyl derivative.
Other metabolites found were 5,6-dihydro-5,6-dihydroxy-, 4-hydroxy-,
and 5-hydroxy-carbaryl. Appreciable cleavage was obtained with
β-glucosidase, β-glucuronidase, and glusulase. Ether-solubles recovered
after hydrolysis included N-hydroxymethyl-, 5,6-dihydro-5,6-dihydroxy-,
4-hydroxy-,and 5-hydroxy-carbaryl; 1-naphthol; and minor unknowns
(Kuhr, 1971).

In Egyptian cotton leafworm (Spodoptera littoralis Boisduval), carbaryl
was converted to three metabolites which appeared to be conjugates. No
carbaryl or 1-naphthol was detected in the excreta extraction (Hanna
and Atallah, 1971).

In metabolism of carbaryl by tissues of the blowfly larva(Calliphora
erythrocephala), metabolism by fat body was more rapid than by cutaneous
muscle or gut. There was no detectable metabolism by cuticle or by
haemolymph. Four metabolites were separated. Two were identified as
4-hydroxy and 5-hydroxy-derivatives of carbaryl. The other two were
tentatively identified as 5,6-dihydrodihydroxy- and N-hydroxymethyl-
derivatives (Price and Kuhr, 1969).

The engorged adult female cattle tick(Boophilus microplus)was injected
with carbaryl. Major metabolic pathways included carbamate hydrolysis,
hydroxylation, and conjugation. The hydrolytic step was virtually
complete 21 hours after dosing. About 90% of the ring label was
recovered following administration of ring-labeled carbaryl. Conjugates
of 1-naphthol and 1,5-dihydroxynaphthalene were found. The presence

of a conjugate of 5,6-dihydro-1,5,6-trihydroxynaphthalene was also
indicated (Bend et al., 1970).

A susceptible strain and three organophosphorus- and carbamate-
resistant strains of cattle tick larvae (Boophilus microplus)
were topically treated with labeled carbaryl. Penetration was
rapid and virtually completed within 6 hours. Quantitative dif-
ferences were observed. Three metabolites were isolated. One
was identified by infra-red spectroscopy as 5,6-dihydrodihydroxy-
carbaryl. This was metabolized to another compound thought to be
5,6,7,8-tetrahydrotetrahydroxy-1-naphthyl-N-methylcarbamate. The
third compound was not identified. Some CO_2 was also observed
(Schuntner et al., 1971).

In the silkworm (Bombyx mori), some CO_2 was released and a metabolite
was identified as 2-hydroxycarbaryl (Moriyama et al., 1972). Several
other metabolites were observed but not identified (Sugiyama et al.,
1971).

A mosquito larval enzyme system requiring $NADPH_2$ was obtained from
resistant Culex fatigans. When carbaryl was incubated with this
system, 4-hydroxy- and 5-hydroxy-carbaryl, 1-naphthol, and three
unknowns were observed (Shrivastava, 1971).

In corn, wheat, rice, snap beans, potato, tomato and alfalfa plants,
metabolic products of carbaryl were qualitatively similar but dif-
fered quantitatively. Inside the plant, carbaryl was transformed
by oxidation and hydrolysis to products which were rapidly converted
to water soluble glycosides (Andrawes and Chancey, 1972).

After injection into bean plants, carbaryl was metabolized into
water soluble products and products which could not be extracted
from plant tissues. After acid hydrolyses of water-soluble
metabolites, the following compounds were identified: 1-naphthol,
4- and 5-hydroxy carbaryl, and N-hydroxymethyl carbaryl (Dorough
and Wiggins, 1969). The presence of these metabolites was also
observed in peas, peppers, and corn after injection of carbaryl
into the plants (Mumma et al., 1971).

Labeled carbaryl was incubated with tobacco cells. In addition to
unchanged carbaryl, α-naphthol and 5,6-dihydro-5,6-dihydroxycarbaryl
were present. N-O conjugates of N-hydroxycarbaryl and other unidenti-
fied conjugates were also present (Locke et al., 1971).

Under conditions similar to those in the field, the principal non-
biological degradation pathway of carbaryl in water involved base-
catalyzed hydrolysis to 1-naphthol followed by photolytic decomposi-
tion of 1-naphthoxide ion (Wauchope and Haque, 1972).

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In sea water, 1-naphthol underwent degradation and change. The formation of CO_2 was observed but was probably produced by microorganisms. Exposure to light enhanced CO_2 production. A reddish-blue precipitate also formed. Four peaks were obtained on the total ion monitor of a mass spectrometer. One peak was completely assigned to 1,4-naphthoquinone. The presence of 2-(or 3)-hydroxy-1,4-naphthoquinone, and 1-naphthol were also observed. Identification of the intact compound was not made (Lamberton and Claeys, 1970).

In estuarine water and mud in laboratory aquaria, carbaryl was degraded to 1-naphthol. Less than 10% of the combined compounds were present after 10 days (Karinen et al., 1967).

The persistence of carbaryl at concentrations of 2 and 200 ppm in five different Japanese rice paddy soils was studied. Evolution of CO_2 was not rapid and varied between 2% and 40% over a 32 day test period. Hydrolysis of the carbonyl linkage was the dominant metabolic pathway. An isolated soil microorganism rapidly degraded naphthol and produced a number of unidentified aromatic compounds (Kazano et al., 1971).

Carbaryl was incubated with a soil bacteria, not identified. Chromatography showed four spots in addition to carbaryl (Tewfik and Hamdi, 1970). With three soil isolates capable of accelerating carbaryl hydrolysis to 1-naphthol, Sevin and 1-naphthol were more resistant to transformation in pure cultures than in mixtures of the investigated microorganisms (Bollag and Liu, 1971).

Soil microorganisms metabolized carbaryl to compounds which chromatographed as 1-naphthyl N-hydroxymethylcarbamate, 4-hydroxy-1-naphthyl N-methylcarbamate and 5-hydroxy-1-naphthyl N-methylcarbamate. 1-naphthol was metabolized by Pseudomonas sp. Four metabolites were produced and one was identified as coumarin (Kazano et al., 1972).

Carbaryl was added aseptically to an autoclaved media which was then inoculated with a spore suspension of the fungus Gliocladium roseum. Three metabolites were isolated by TLC and identified as N-hydroxy-, 4-hydroxy- and 5-hydroxy-carbaryl by UV, IR, and mass spectroscopy (Liu and Bollag, 1971).

When exposed to Aspergillus terreus, carbaryl was metabolized to four compounds which were identified as 4-hydroxy- and 5-hydroxy-1-naphthyl-N-methyl carbamate, 1-naphthyl-N-hydroxymethyl carbamate and 1-naphthyl carbamate. The latter two were decomposed to 1-naphthol when incubated with the fungus (Liu and Bollag, 1971 and 1972a).

Other microorganisms have been observed to be capable of degrading carbaryl to naphthol. In a mixed culture, Fusarium solani hydrolyzed carbaryl to 1-naphthol and the bacterial coccus degraded the radioactivity

of the ring-labeled l-naphthol (Bollag and Liu, 1970). In other
studies, Fusarium solani also degraded l-naphthol but no inter-
mediates were identified (Bollag and Liu, 1972b).

Soil fungi were isolated from carbaryl treated soil and then incubated
with labeled carbaryl. The degradation of carbaryl was followed by
thin-layer chromatography. Most of the fungi investigated were able
to hydroxylate carbaryl. The products, however, varied both qualita-
tively as well as quantitatively with various fungi. Except Aspergillus
fumigatus, all the Aspergillus species were able to hydroxylate
carbaryl. The major metabolite was l-naphthyl N-hydroxymethylcarbamate
(1). In contrast to this, isolates of Penicillium species (Mucor sp.
and Rhizopus sp.) showed stronger tendency to ring-hydroxylation of
carbaryl and only weak ability for side-chain hydroxylation. Metabolites
from the Penicillium sp. were identified as the 4-hydroxy-(2) and 5-hydroxy-
(3) analogs of carbaryl (Bollag and Liu, 1972a).

	Hydroxylated metabolite formed		
Fungus	1	2	3
Aspergillus flavus Link ex Fries	+	+	+
fumigatus Fresenius	–	–	–
niger Van Tieghem	+	+	+
terreus Thom.	+	+	+
sp.	+	+	+
Fusarium oxysporum Schlectendahl	–	–	–
roseum Link	+	–	–
sp.	–	–	–
Geotrichum candidum Link	–	–	–
Gliocladium roseum (Link) Thom.	+	+	+
Helminthosporium sp.	+	+	+
Mucor racemosus Fresenius	+	+	+
Penicillium roqueforti Thom.	–	–	–
sp. (isolate 1)	+	–	–
sp. (isolate 2)	+	+	+
Rhizopus sp.	+	+	+
Trichoderma viride Per. ex Fries	+	+	+

(Bollag and Liu, 1972a)

<u>CARBOFURAN</u> (Furadan, NIA 10242) [<u>N</u>-Methyl-2,3-dihydro-2,2-dimethyl-
7-benzofuranylcarbamate]

The fate of carbofuran was observed after administration to a
hen. In the liver, compounds II, III and IV were observed in
free and conjugated forms. In feces, in addition to the foregoing,
compounds VI, VII, VIII and IX and five unknown compounds were
found (Hicks et al., 1970).

Mouse liver enzyme preparations degraded carbofuran to at least
seven organo-soluble metabolites. Three were identified:
3-hydroxy carbofuran, 3-keto carbofuran, and <u>N</u>-hydroxymethyl
carbofuran (Shrivastava et al., 1970).

Alfalfa, containing carbofuran residues in the form of glycosides
of 3-hydroxycarbofuran (V), 2,3-dihydro-3,7-dihydroxy-2,2-
dimethylbenzofuran (XIII) and 2,3-dihydro-7-hydroxy-2,2-dimethyl-3-
oxobenzofuran (XIV) was fed to rats. Urine contained the glucuronides
and sulfate compounds XIII, XIV, XXI and XXII and the glucuronide of
3-hydroxycarbofuran (V). Carbofuran was metabolized and excreted
as the glucuronides and sulfates: compounds V, XII, XIII, XX, and
XXI (Knaak et al., 1969).

When carbofuran was given to a cow, it was hydrolyzed and excreted
in urine primarily as carbofuran phenol sulfate and glucuronide.
Small amounts of the glucuronides and sulfates of the 3,7-diol
and 3-keto-7-phenol and the glucuronide of 3-hydroxy carbofuran
were also excreted. In milk, 3-hydroxy carbofuran was observed
after acid hydrolysis. Alfalfa containing carbofuran residues was
administered to a cow. These residues were metabolized and excreted
as sulfates of 3-keto-7-phenol (65%), the 7-phenol (9.4%) and the
3,7-diol (6.4%). The glucuronides of these phenols (11%) were also
present (Knaak et al., 1970). When carbonyl labeled carbofuran was
fed to a cow, the milk contained labeled materials resulting from
incorporation of the $^{14}CO_2$ (Dorough and Ivie, 1968).

Twenty-one days after application of carbofuran at the rate of
0.5 lb AI/A to alfalfa there was no detectable residue of carbofuran.
The metabolite 3-hydroxycarbofuran was present at a level of 0.55 ppm
(Shaw et al., 1969). After application of carbofuran to the soil
of potted alfalfa plants, eight metabolites were observed. Four

were glycosides from which, after acid hydrolysis, the following aglycones were obtained: Carbofuran phenol, 3-ketophenol, 3-hydroxy-phenol, and 3-hydroxycarbofuran. These compounds were also found in the unbound state. Studies indicated that two of the glycosides contained monosaccharides; another contained a disaccharide (Knaak et al., 1970).

In corn plants exposed to carbofuran, only 3-hydroxycarbofuran and its glycoside were observed (Cook et al., 1969). Tobacco plants were exposed to carbofuran by root absorption. In the leaves, the half-life was about 4 days and carbofuran was progressively metabolized to 3-hydroxy carbofuran and 3-ketocarbofuran. These two metabolites and carbofuran were also hydrolyzed to their corresponding phenols. All four hydroxy compounds were conjugated as glycosides. When carbofuran was applied topically to tobacco leaves, the half-life was considerably more than 4 days. Whereas 3-hydroxy-carbofuran was the major metabolite after root treatment, the hydrolysis product carbofuran phenol was the major unconjugated metabolite after topical leaf application (Ashworth and Sheets, 1972).

I=Insects   M=Mammals   P=Plants
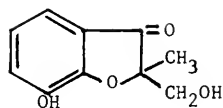
2-Hydroxymethyl-
3-ketofuradan
phenol(XIX)

2-Hydroxymethyl-
3-ketofuradan
(XVIII)
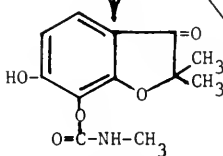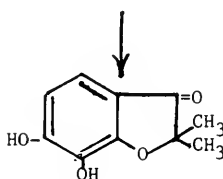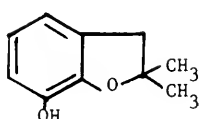
Furadan Phenol (VI)

Glucuronide(XII)

Sulfate(XX)

N-Hydroxymethyl
Furadan (II)

Furadan (I)

3-Ketofuradan
(VIII)

3-Hydroxyfuradan
(IV)

Glycoside
(V)

Conjugate
(XI)
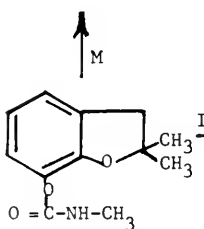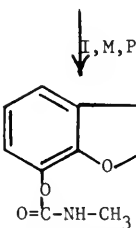
3-Hydroxy-N-hydroxy-
methyl furadan (III)
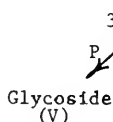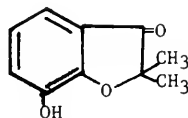
3-Keto-6-hydroxy-
furadan (X)

Glucuronide(XIII)

Sulfate (XXI)

3-Hydroxyfuradan
phenol(VII)

3-Keto-furadan
phenol (IX)
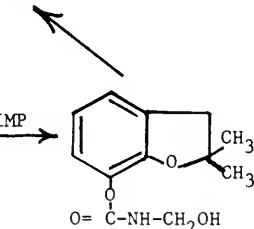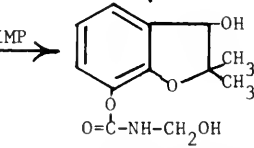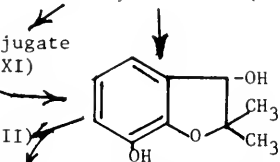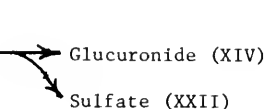
Glucuronide (XIV)

Sulfate (XXII)

3-Keto-6,7-dihydroxy-
furadan(XVI)

81

CARBOXIN   (Vitavax, DMOC)   [5,6-Dihydro-2-methyl-1,4-oxathiin-3-carboxanilide]

In dogs fed carboxin, oxidation to the sulfoxide occurred in the digestive tract (Chin et al., 1969).

Cotton seedlings were treated with carboxin. Chromatography of the hypocotyls indicated the presence of seven materials. In addition to unchanged carboxin, three metabolites were found; 2,3-dihydro-5-carboxanilido-6-methyl-1,4-oxathiin-4,4-dioxide; a hydrolysis product of DMOC; and an aniline derivative (Allan and Sinclair, 1969).

When used to treat barley and wheat seeds, Carboxin was absorbed by the seedlings and oxidized mainly to the sulfoxide. Some sulfone was also found. As plants reached maturity, anilide complexes increased in precentage (Chin et al., 1969 and 1970a).

In soil, carboxin was oxidized to the sulfoxide. No sulfone was detected. The sulfoxide also formed under sterile conditions. The sulfoxide was formed in water. At pH of 2 and 4, slow oxidation to the sulfone was detected. No hydrolysis was observed (Chin et al., 1969 and 1970b).

(See also Oxycarboxin)

Carboxin

Oxycarboxin
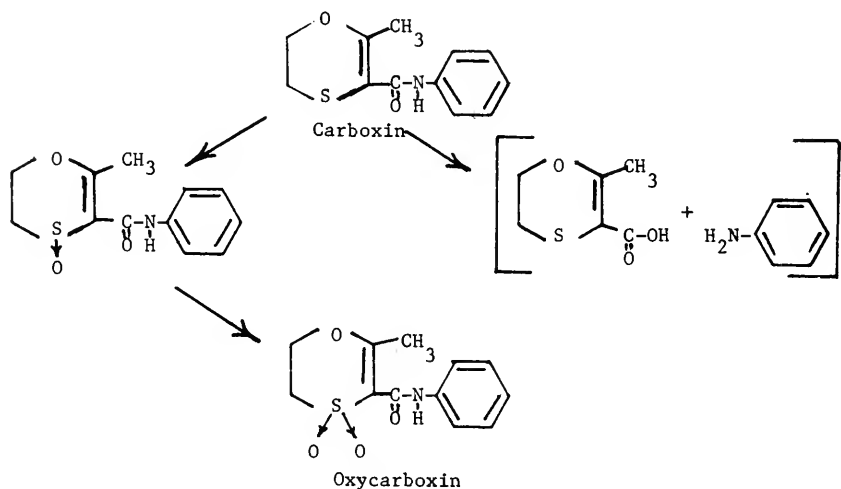
<u>CCC</u> [2-Chloroethyl trimethylammonium chloride]

Winter barley (<u>Hordeum</u> <u>vulgare</u>) weakly metabolized CCC. After labeled material was used, radioactivity was found in the choline moiety of phosphatidyl choline. Traces of radioactivity were found in other unidentified ethanol soluble compounds as well as choline (Belzile et al., 1972).

Cela W-524 decomposed upon heat sterilization. Chromatography indicated the presence of N-formylpiperazine, piperazine, and an unidentified compound.

Degradation products in plants were not identified (Fuchs et al., 1971).

CEPA   (Amchem 66-329, Ethrel, Ethephon)   [2-Chloroethylphosphonic Acid]
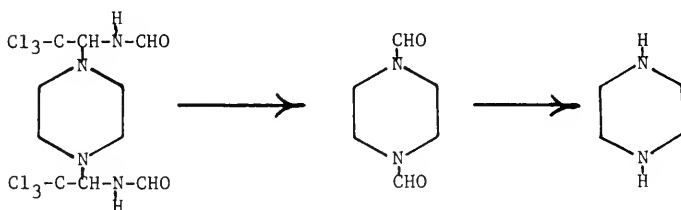
In the presence of base, CEPA broke down with the evolution of
ethylene. The reaction appeared to be a second order type and
also led to production of phosphonate and chloride. After
exposure of plants to CEPA, ethylene was evolved. Phosphate
and chloride were also detected (Warner and Leopold, 1969;
Yang, 1969).

Mature green tomatoes were allowed to ripen under an atmosphere
of N_2. There was little or no production of ethylene from the
control fruit. From CEPA-treated fruit, there was a significant
increase in ethylene production (Lougheed & Franklin, 1970).

Within 12 hours after application of CEPA to leaf surfaces of
apple and cherry trees, ethylene was detected (Moyer et al.,
1972). CEPA in leaves, hull, shell and kernel of walnuts was
also metabolized (Martin et al., 1972).

Chlordane and Related Compounds

α - (or cis-) chlordane

1-exo,2-exo,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene

γ - (or trans-) chlordane

1-exo,2-endo,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene

Chlordene

4,5,6,7,8,8-hexachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene

Chlordene epoxide

4,5,6,7,8,8-hexachloro-exo-(cis)-2,3-epoxy-3a,4,7,7a-tetrahydro-4,7-methanoindene [also an endo-(trans)-2,3-epoxy- isomer].

Oxychlordane

1-exo,2-endo,4,5,6,7,8,8-octachloro-2,3-exo-epoxy-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene

Heptachlor

1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene

Male rabbits were fed trans-chlordane-^{14}C for 10 weeks. Feces and urine were collected during this period and for two additional weeks. By the end of 12 weeks, 70% of the total administered material had been excreted. From the urine, one metabolite was isolated in crystalline form and identified as the chlorohydrin obtained from perbenzoic acid epoxide of chlordene (Poonawalla and Korte, 1971).

In the pesticide residue analyses of milk from cows feeding on alfalfa contaminated with chlordane, a major component of the residue was not typical of chlordane. A similar residue was found in cheese made from milk of cows fed technical chlordane. By means of mass and infrared spectrometry and synthesis, the compound was identified as an epoxide of chlordane, m.p. 98-101°C. (uncorrected) (Lawrence et al., 1970). From the fat of pigs fed α- or γ- chlordane, a non-polar metabolite was isolated and identified as the epoxide, oxychlordane, m.p. 99-101°C. (uncorrected) (Schwemmer et al., 1970).

After feeding γ-(trans) and α-(cis) chlordane to rats, pigs, cattle and beagle dogs, a compound was isolated and identified by elemental analysis, NMR, IR and synthesis as oxychlordane. Other studies indicated that, after 15 days on a diet containing pure trans-chlordane, rats of both sexes stored more oxychlordane than when fed the cis-isomer. It was also observed that storage in females was higher than in males. In vitro this metabolism proceeded more readily with liver from rats pretreated with p,p^1-DDT, dieldrin, γ-chlordane, or heptabarbital than with liver from normal rats. Another metabolite, identified as 1-exo-2-endo-dichlorochlordene, was also formed and data indicated that this was an intermediate in the oxychlordane pathway (Polen et al., 1971; Street and Blau, 1971 a and b, 1972).

Microsome from flies, pig, rabbit and rat liver oxidized each chlordene epoxide into a corresponding diol (Brooks et al., 1970).

^{14}C-labeled trans-chlordane in acetone was applied to leaves of young cabbage plants. Analyses of plant parts was made at 4 and 10 weeks. Carrots were planted in soil treated with trans-chlordane-^{14}C and analyzed after 12 weeks. In both cases, three metabolites were observed. One of the metabolites was isolated from cabbage plants and identified by gas chromatography and mass spectroscopy as dihydroxy-β-dihydroheptachlor (Kaul et al., 1972 a,b).

Trans-chlordane (γ-isomer) was altered by UV irradiation. The cis-chlordane (α-isomer) underwent change to the extent of 65-69% in air in 16-20 hours of UV irradiation; in aqueous methanol, 38-41% in 36 hours; and in aqueous dioxane, 38-40% in 16-20 hours (Benson et al., 1969; Ivie et al., 1972;Vollner et al., 1969).

When chlordene was irradiated in hexane, a mono- and a di- dechlorinated product was formed. In acetone, chlordene and the two dechlorinated compounds formed their respective cage molecules. Heptachlor and isoheptachlor were formed by irradiation in n-hexane

Chlordane
(trans)

Photo-trans-chlordane

1-Hydroxychlordane

Oxychlordane

1,2-Dichlorochlordene

cis-Chlordane

Photochlordane

Chlordene

Chlordene
epoxide

Chlordenediol

1-Hydroxychlordene

1-Hydroxy-2,3-epoxychlordene
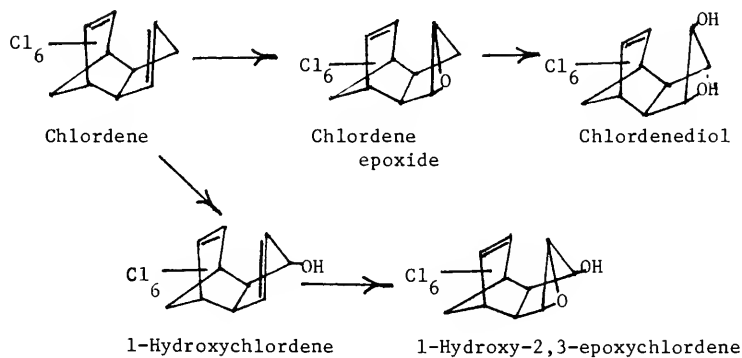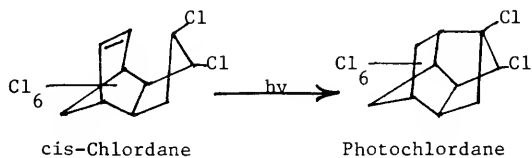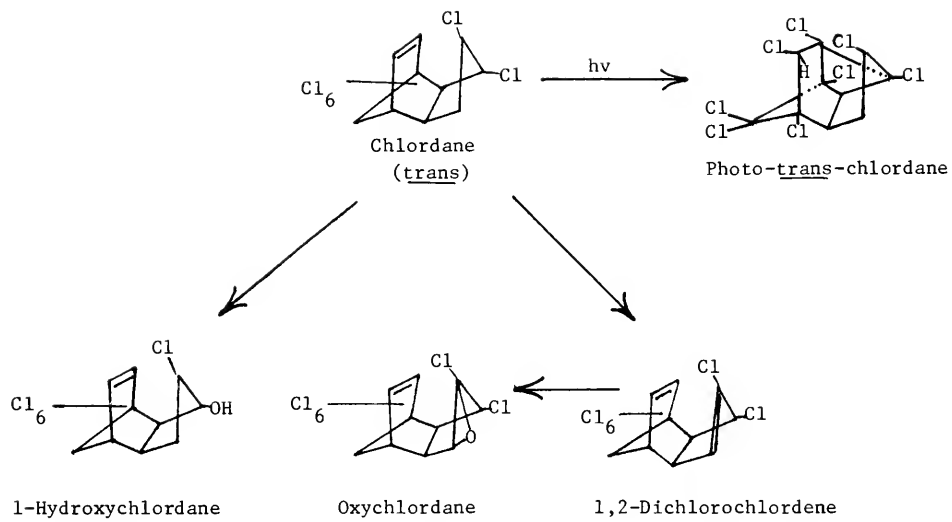
by a radical "Transfer-mechanisms." By intermolecular 1,2-photocyclo-addition the dimer was formed. Finally, with ring opening of heptachlor and isoheptachlor, two additional compounds were formed (Parlor and Korte, 1972). In air, chlordene underwent 74-76% change in 16 hours when irradiated with UV; 28-30% in 16 hours in aqueous methanol (Vollner et al., 1969).

In rats heptachlor was metabolized to the epoxide. The epoxide was in turn metabolized to the 1-hydroxyepoxide (Kaul et al., 1970).

Heptachlor epoxide was fed to male albino rats. Feces were collected and extracted. Thin-layer chromatography separated 1-hydroxy-2,3-epoxychlordene from another metabolite. Mass spectrum and nuclear magnetic resonance spectrum indicated a dehydrogenated derivative. Hydrogenation gave 1-hydroxy-2,3-epoxychlordene (Matsumura and Nelson, 1971).

Incubation of heptachlor epoxide m.p. 160°C (HE 160) with microsomal preparations from houseflies and livers of pigs and rabbits gave rise to a diol. When the levorotatory heptachlor epoxide m.p. 90°C was incubated, hydration to a mixture of diols occurred. The preponderant diol appeared to be identical with that arising from HE 160 (Brooks and Harrison, 1969; Brooks et al., 1970).

In soil numerous organisms were found able to degrade heptachlor by epoxidation, hydrolysis and reduction. Incubation of heptachlor with a mixed culture of soil organisms gave rise to chlordene which was further metabolized to chlordene epoxide. 1-Hydroxychlordene, 1-hydroxy-2,3-epoxychlordene, and heptachlor epoxide have been found also. In water, heptachlor hydrolyzed chemically to 1-hydroxychlordene. Soil organisms were capable of metabolizing this to hydroxy-epoxy. This may be further metabolized to what is believed to be ketochlordene (Carter et al., 1971; Miles et al., 1969, 1971).

Several years after a heptachlor formulation was applied to soil, in addition to heptachlor, heptachlor epoxide, chlordene, 1-hydroxychlordene, α- and γ-chlordane, and nonachlor were isolated from the soil and detected by thin-layer chromatography. Three unidentified compounds were also detected. Chlordane and nonachlor were probably present in the formulation used (Bowman et al., 1965; Carter and Stringer, 1970; Duffy and Wong, 1967; Lichtenstein et al., 1970).

After exposure of heptachlor epoxide in acetone or on bean plants in the presence of rotenone, a ketonic photoproduct isomeric with heptachlor epoxide was isolated, characterized, and identified as photoheptachlor epoxide I. A second compound isolated from the reaction was identified as photoheptachlor epoxide II. The latter was also produced by irradiation of photoheptachlor epoxide I (Ivie et al., 1972).

Photoheptachlor I

Photoheptachlor II

Monodechlorination

Photoheptachlor III
(Cage)

Heptachlor

Heptachlor-cyclohexane Adduct

Plants, Animals
Microorganisms

Heptachlor Epoxide

Photoheptachlor "Epoxide"
I

Photoheptachlor Epoxide
II

cis -Nonachlor

Photo-cis-Nonachlor

trans-Nonachlor

Photo-trans-Nonachlor
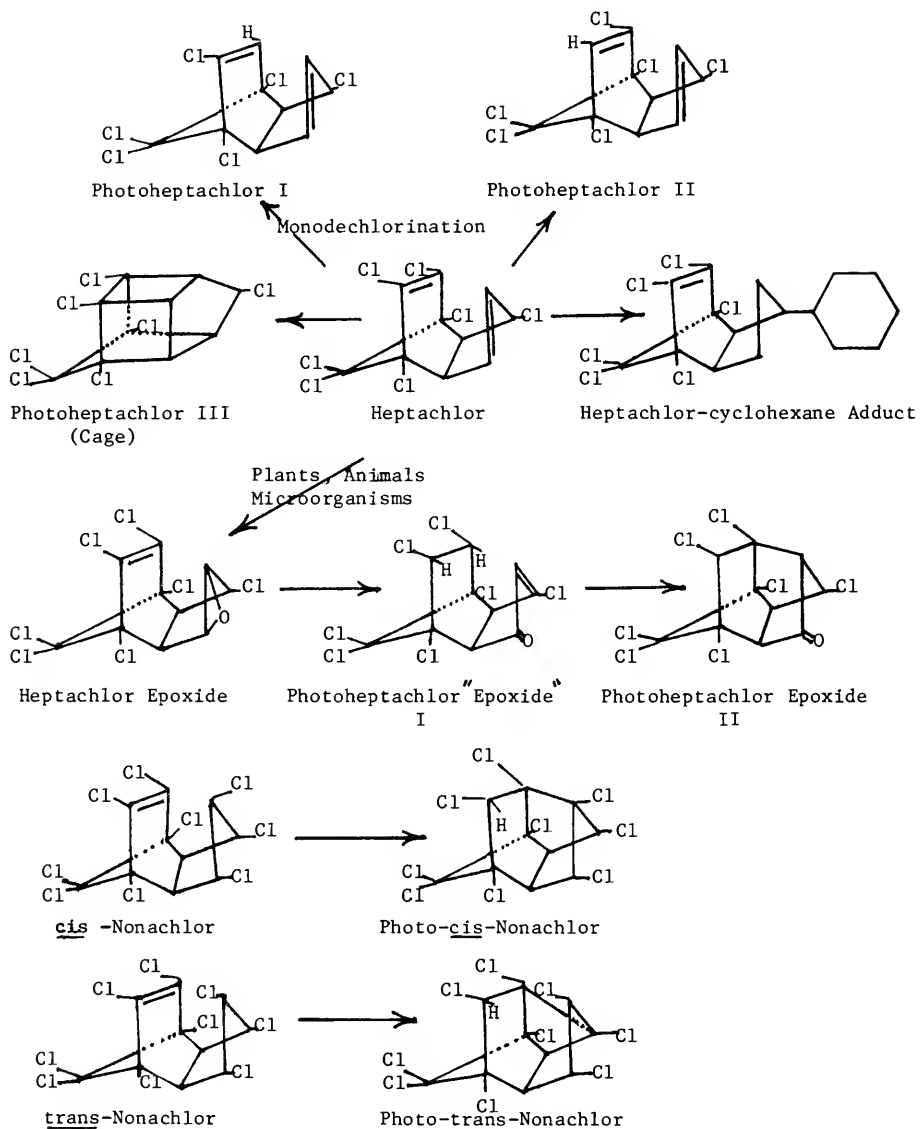
After application of heptachlor to algae (<u>Chlorella</u> pyrenoidosa) in nutrient solution, the algae contained heptachlor epoxide (HE) (68% of the extractable radioactivity) and a metabolite (7% of extractable radioactivity) which was less polar than HE. This metabolite was identified by chromatography, synthesis and mass spectroscopy as 4,5,6,7,8,8-hexachloro-2,3-epoxy-4,7-methano-3a,4,7,7a-tetrahydroindan-1-one. Three other metabolites were observed but not identified. (Elsner et al., 1972).

Labeled heptachlor was applied to cabbage and to the soil. Analyses of the plant material indicated the presence of 1-hydroxychlordene, heptachlor epoxide and a metabolite less hydrophylic than heptachlor epoxide. In soil, only 1-hydroxychlordene was observed. Similar results were obtained in wheat. The studies indicated formation of 1-hydroxychlordene in soil and its uptake by plants, wherein it was converted to hydrophylic products (Weisgerber et al., 1972).

Heptachlor

Heptachlor Epoxide

Keto-epoxide

91

Photoheptachlor   Photoheptachlor "Epoxide"

Heptachlor   Heptachlor Epoxide   "diol"

Chlordene   1-Hydroxychlordene   1-Hydroxy-2,3-epoxy-
chlordene

Chlordene Epoxide   "keto" Chlordane(?)

92
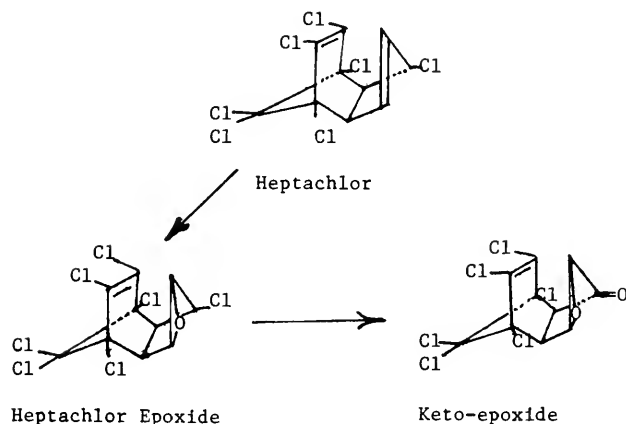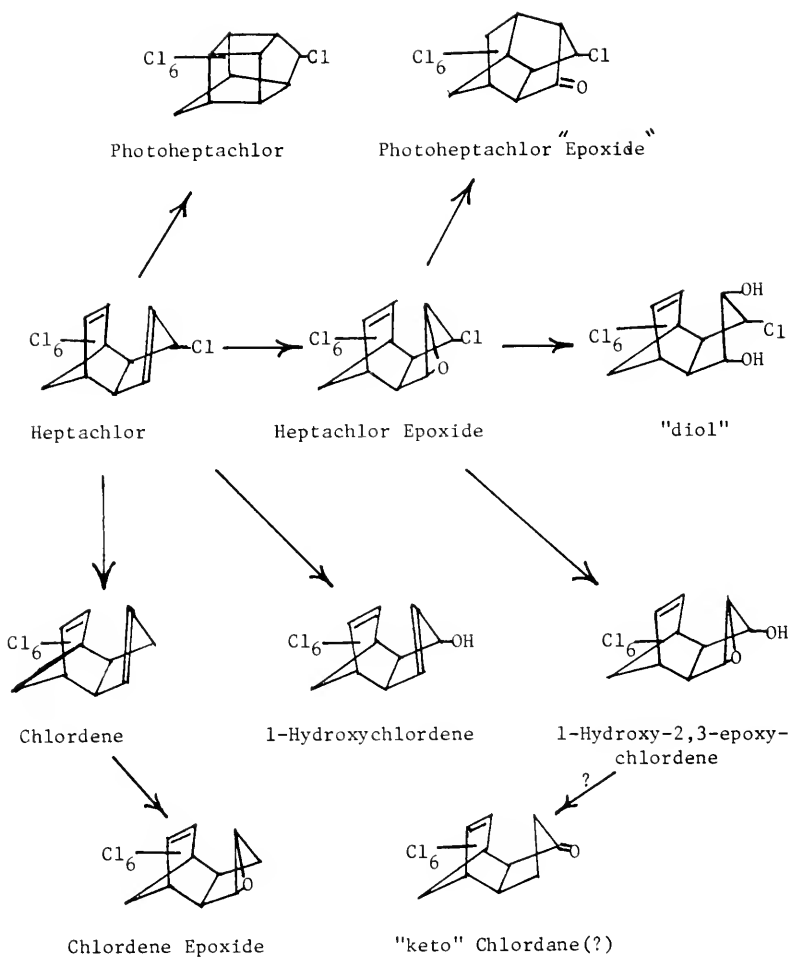
Soil Microorganisms Capable of Degrading Heptachlor
(Miles et al., 1969)

15 species of Trichoderma	16 species of Nocardia
11 species of Penicillium	7 species of Streptomyces
16 species of Fusarium	3 species of Thermoactinomyces
2 species of Aspergillus	1 species of Micromonospora
2 species of Rhizopus	12 species of Bacillus
1 species of Mucor	5 species of Arthrobacter
	1 species of Corynebacterium

In other studies, 1-hydroxychlordene was found in soil treated with heptachlor and in plants grown therein. Some fish taken from a river and lake fed by the run-off of a heptachlor-treated area also contained low levels of the same metabolite (Bonderman and Slach, 1972).

The photolysis of heptachlor has been studied in several solvents. In hexane, the monodechlorination products are obtained. When the photolysis was carried out in mixtures of cyclohexane and acetone, the cyclohexyl adduct was obtained. In acetone solution, photolysis of heptachlor gave the cage compound (McGuire et al., 1970 and 1972. Similarly, in benzene solution containing benzophenone, the cage compound was obtained after irradiation of heptachlor (Rosen and Siewierski, 1970). UV irradiation in aqueous methanol caused about 90% change in 16-20 hours; 88% change in 16 hours in aqueous dioxane (Vollner et al., 1969). Results of other studies have been summarized and diagramed (Benson et al., 1971; Fischler and Korte, 1969; Parlar and Korte, 1972).

After intravenous administration of labeled β-dihydroheptachlor (β-DHC) to male rats, 60% and 70% of the radioactivity was excreted in 24 and 48 hours, respectively, in the feces as hydrophylic metabolites primarily. The radioactivity in the fatty tissues after 48 hours was about 75-90% metabolites and the remainder was unchanged β-DHC. Four metabolites were detected by TLC; and two were identified as the trans-diol and chlorohydrin (Kaul et al., 1970).

COMPOUND	PHASE	UV	FILTER	PHOTOPRODUCT
cis-Chlordane	Acetone	20 hr	Pyrex	IV(80%)
	Dioxane/ Water	3	Quartz	II,IIa(65%) III(15%);IV(10%)
		19	Quartz	III(96%);IV(2%)
	Ligroin	20	Quartz (λ=254)	II,IIa(30%);III(20%) IV(4%);V,Va(26%) VI(10%)
trans-Chlordane	Dioxane/ Water	6	Quartz	VIII,VIIIa(62%)
		45	Quartz	IX(85%)
Heptachlor	Methanol/ Water	4	Quartz	XII,XIIa(60%)
	Gas (N_2)	240	Pyrex	XI(12%)
	Gas (O_2)	7 wk	Quartz	XI(10%);XIII(6%) XIV(7.5%)
	Gas (AIR)	48 hr	Pyrex	XI(2.5%)
Nonachlor	Dioxane/ Water	15	Quartz	XVI(90%)
Cmpd XVI	Dioxane/ Water	22	Quartz	XVII(85%)
β-Dihydrohepta- chlor	Ligroin	80	Quartz	XIX(8%); XX(60%) XXI(25%)
	Acetone	20	Pyrex	XIX(8%)
Cmpd XX	Acetone	12	Quartz	XXII(40%)
Cmpd XXI	Acetone	126	Quartz	XXIII(80%)
Chlordene	Acetone	60	Quartz	XXV(30%)
		70	Quartz	XXVI,XXVII(55%) XXV(20%);XXIX(11%)

(Vollner et al., 1971)

(IV)   cis-Chlordane(I)   (IIa)

(II)   (III)   (V)

(Va)   (VI)

trans-Chlordane
(VII)

(VIII)   (VIIIa)

(IX)

(H)Cl
Cl(H)
Cl
Cl
Cl
Cl
(XII & XIIa)

Cl
Cl
Cl
Cl
Cl
Cl
(X)
Heptachlor

Cl
Cl
Cl
Cl
Cl
Cl
Cl
(XI)

Cl
Cl
Cl
Cl
Cl
Cl
Cl
(XIII)

Cl
Cl
Cl
Cl
Cl
Cl
OH(Cl)
Cl(OH)
(XIV)

Cl
Cl
Cl
Cl
Cl
Cl
Cl
(XV)
Nonachlor

Cl
H
C₇
(XVI)

H
H
C₇
(XVII)

H
H
Cl
Cl
Cl
Cl
(XXI)

Cl
H
Cl
Cl
Cl
Cl
(XX)

H
H
Cl
Cl
Cl
Cl
(XXII)

H
H
H
Cl
Cl
Cl
(XXIII)

Cl
Cl
Cl
Cl
Cl
Cl
(XVIII)
β-Dihydroheptachlor

Cl
Cl
Cl
Cl
Cl
Cl
(XIX)

96
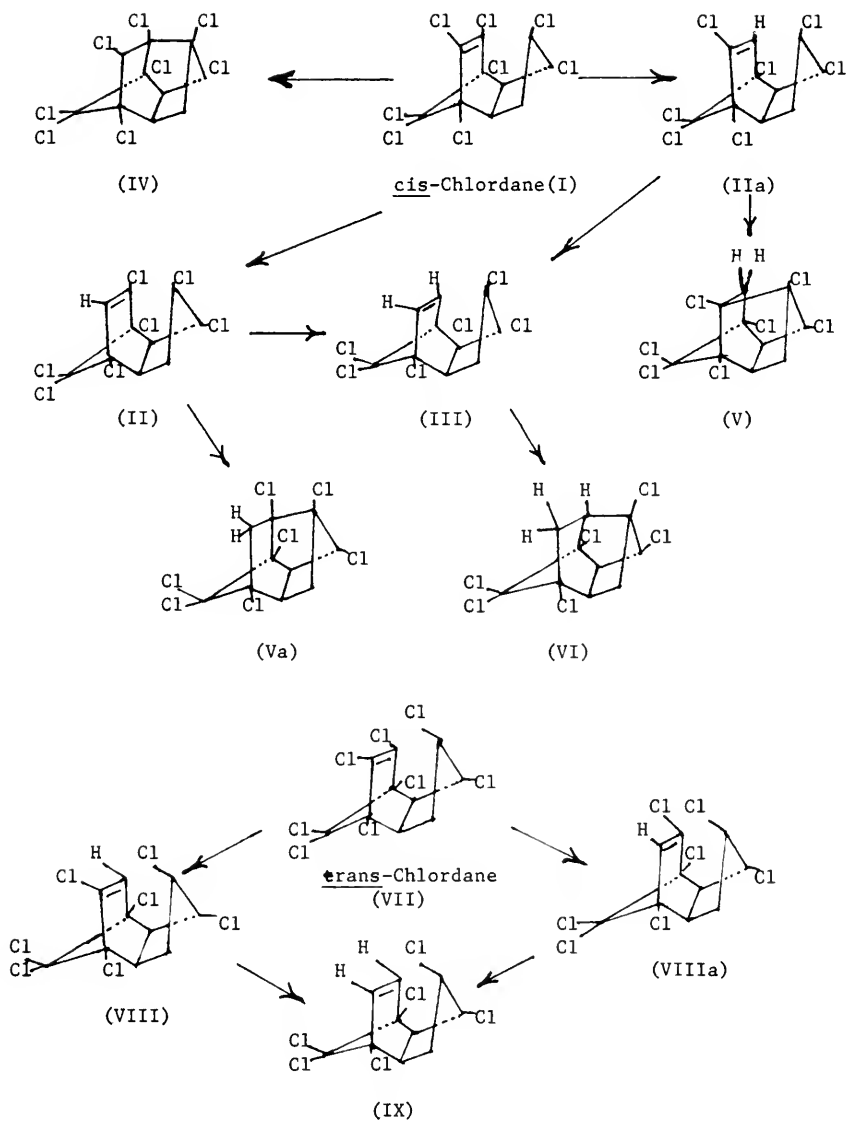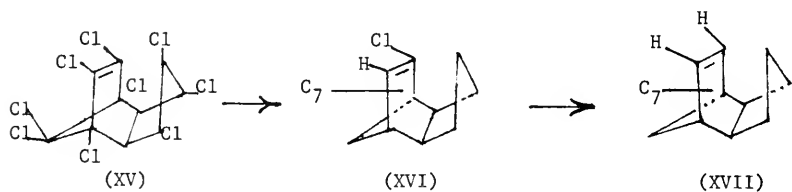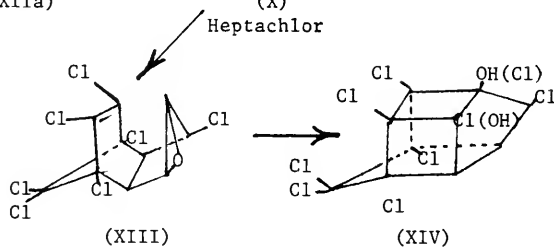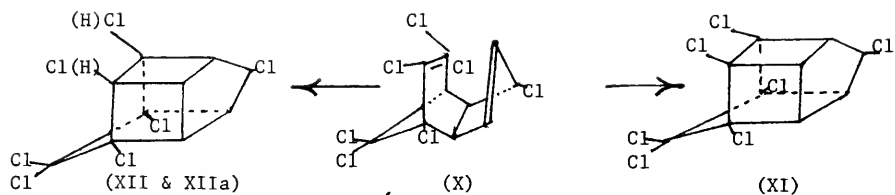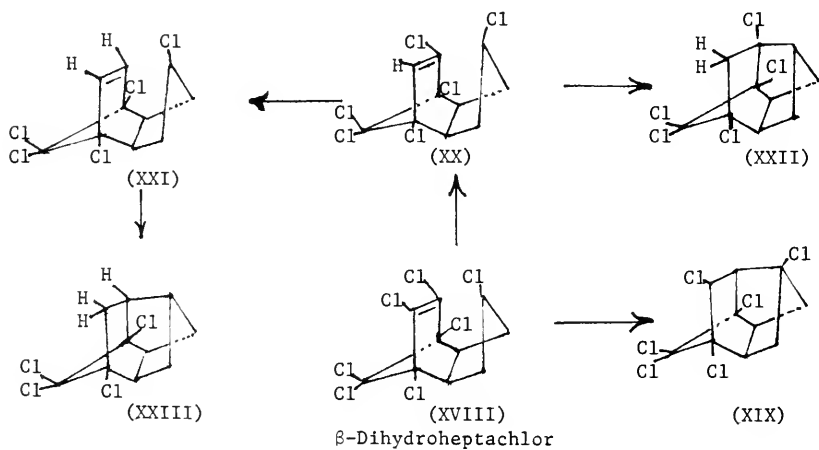
CHLORDENE

REPORTED PHOTOCHEMICAL REACTIONS
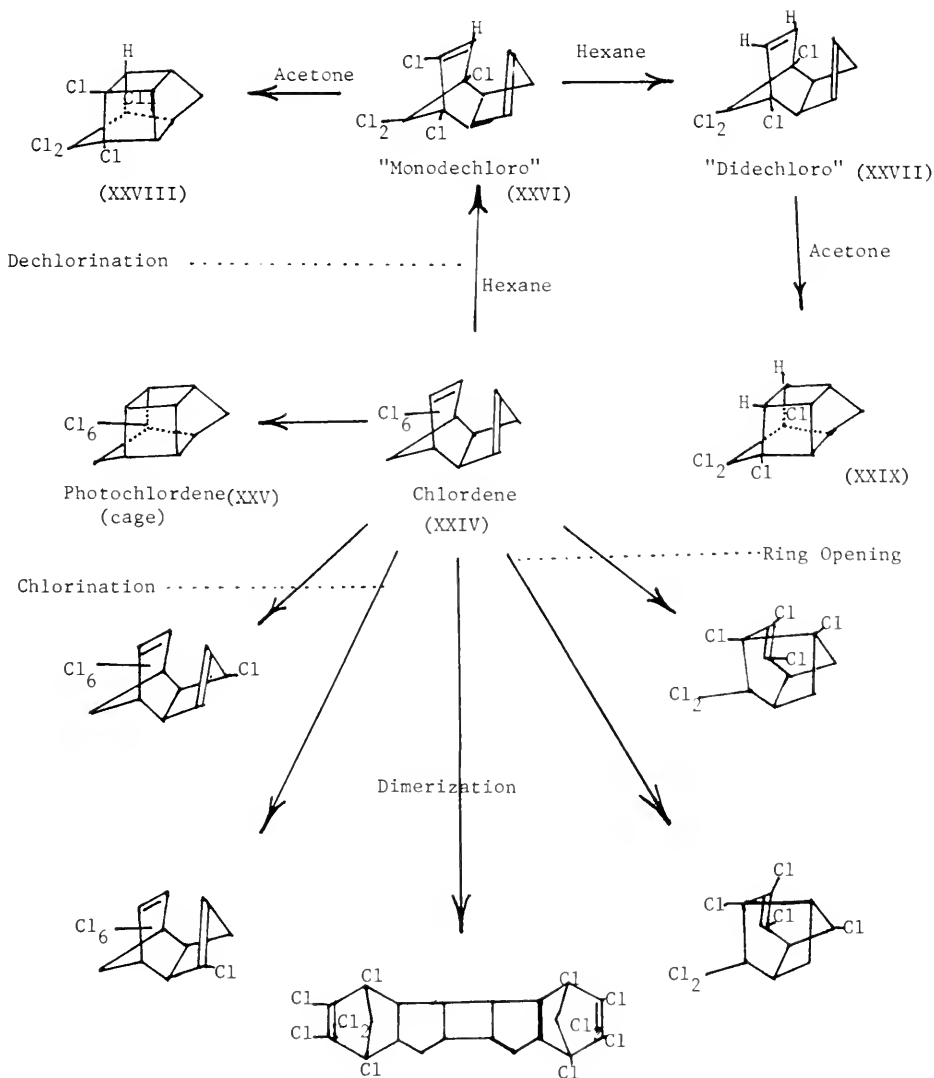
CHLORDIMEFORM (Chlorphenamidine, Galecron, Fundal, C-8514, EP-333, Schering -36268) ['-(4-Chloro-o-tolyl)-N,N-dimethyl-formamidine]

Labelled galecron was administered to a dog and goat. Analyses of dog and goat urine revealed the presence of demethyl galecron(II), N-formyl-4-chloro-o-toluidine(III) and 4-chloro-o-toluidine(IV), free and conjugated. 5-Chloroanthranilic acid and N-formyl-5-chloroanthranilic acid were also observed in the free state. In addition to these, three unidentified compounds were observed in goat urine in the free state; and six unidentified compounds in dog urine, in the conjugated state. In bile from a treated dog, the major metabolites were II, III and an unidentified compound. At least 50% of the labeled material in bile was in the form of conjugates. Incubation with β-glucuronidase released compounds I, II, III, IV, and two unknowns (Gupta and Knowles, 1970).

Within seventy-two hours after oral administration of Galecron-^{14}C to rats, 88% of the dose was eliminated in the urine. After chloroform extraction, in addition to unchanged galecron, compounds II, III, and IV were identified. It was thought that some 4-chloro-2-methylacetanilide (VII) was also present in addition to three unidentified compounds. In the ethylacetate extract of urine from rats treated with 4-chloro-o-toluidine-^{14}C, several additional compounds were observed: 5-chloroanthranilic acid(VI), 4-chloro-2-methylacetanilide(VII), and 5 unidentified compounds (Knowles amd Gupta, 1970).

Partially purified rat liver formamidase catalyzed the deformylation of 4'-chloro-o-formotoluidide and N-formyl-5-chloroanthranilic acid to 4-chloro-o-toluidine and 5-chloroanthranilic acid, respectively (Ahmad and Knowles, 1971a). Non enzymatic hydrolysis of chlorphenamidine resulted primarily in the N-methyl derivative. In addition to 5 unknown compounds, 4'-chloro-o-formotoluidide and 4-chloro-o-toluidine were observed. Enzymatic degradation of chlorphenamidine by soluble liver enzymes was only slight. However, there was appreciable metabolism of the 4'-chloro-o-formotoluidide by the soluble fraction. Rat liver microsomes rapidly metabolized chlorphenamidine to N-demethylchlorphenamidine, the major metabolite. Considerable amounts of 4'-chloro-o-formotoluidide were also present. With TLC, 5-chloroanthranilic acid was also observed (Ahmad and Knowles, 1971b).

On fruit the persistence of chlordimeform (I) was related directly
to the rate of application and inversely to the number of days after
application. The nature of the fruit surface also exerted an
influence (Ercegovich et al., 1972). Only the parent compound
and N-formyl-4-chloro-o-toluidide were detected in samples of fruit
after spray application of chlordimeform (Witkonton and Erecegovich, 1972).

After application of the acaricide, galecron, to apple seedlings,
degradation occurred at a slow rate. Metabolites characterized were:
N'-(4-chloro-o-tolyl)-N-methylformamidine, N-formyl-(4-chloro-o-
toluidine), and 4-chloro-o-toluidine. The glucoside N-(4-chloro-o-
tolyl)-D-glucosylamine was tentatively identified also (Gupta and
Knowles, 1961). Grapefruit seedlings gave similar results when
treated with galecron (Ehrhardt and Knowles, 1970).

Microbial degradation of galecron was studied with A.aerogenes,
S.marcesens, F. moniliforme, R. nigricans, and S. griseus.
Differences were quantitative, not qualitative. Compounds II, III
and IV were detected. An additional compound was not identified
(Johnson and Knowles, 1970).

Larval cattle ticks (Boophilus microplus), after immersion in aqueous
solutions of labeled chlordimeform, metabolized the acaricide slowly.
Two major metabolites were identifed as N-formyl-4-chloro-o-toluidine
and 4-chloro-o-toluidine. A third compound was characterized only
as a conjugated phenol (Schuntner, 1971).

When galecron was exposed to UV and sunlight, the major product was
N-formyl-4-chloro-o-toluidine. All products were not identified but
one could be 2-methyl-4-chloro-6-hydroxyaniline (Knowles and Gupta,
1969).

Irradiation (at $\lambda > 286$) of aqueous solutions of compound I yielded
N-(4-chloro-o-tolyl) formanidine and bis-4-(N,N-dimethyl-N'-o-
tolylformamidine) ether. The hydrochloride of compound I showed
no reaction even after 12 days (Su and Zabik, 1972a).

N=CH-N CH₃ / CH₃

CH₃

Cl
(I)

M,P,O →

N=CH-N-H / CH₃

CH₃

Cl
(II)

hv
M,P,O,I

M,P,O

N-CHO (H)

CH₃

Cl
(III)

N-Glucosylamine
Conjugate

M,P,O,I

M

NH₂

CH₃

Cl
(IV)

M

HN-CHO

C-OH (O)

Cl
(VI)

M

M

NH₂

C-OH (O)

Cl
(V)

M

HN-C-CH₃ (O)

CH₃

Cl
(VII)

P= Plants
M= Mammals
I= Insects
O= Microorganisms

100
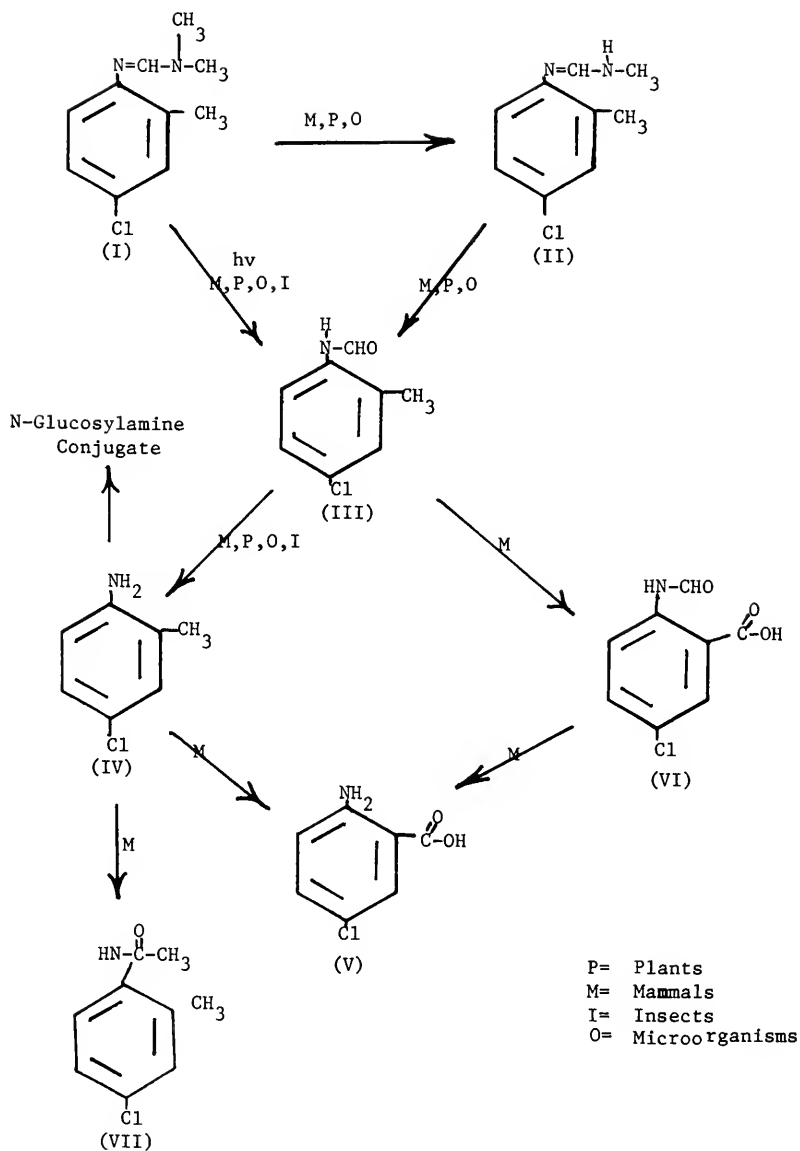
CHLORFENVINPHOS   [Diethyl-2-Chloro-1-(2,4-dichlorophenyl)vinyl phosphate]

Microsomes from rabbit livers were incubated with chlorfenvinphos.
Oxidative cleavage of the ester bond was shown to occur via
hydroxylation at C-1 of one ethyl group to give 1-hydroxyethyl
phosphate triester. This unstable intermediate broke down rapidly
to 2-chloro-1-(2,4-dichlorophenyl) vinyl ethyl hydrogen phosphate.
Oxidative cleavage of the C-O bond, rather than hydrolysis of the
P-O bond, yielded acetaldehyde which was trapped (Donninger et al.,
1967 and 1972).

Chlorfenvinphos was applied to sloping arable land at the rate of
22 kg active ingredient/ha. Only small quantities of the insecticide
appeared at the bottom of the slope. No residues were detected in
a pond at the bottom of the slope at 23 weeks after application
(Edwards et al., 1971). Seven months after application of chlorfenvinphos,
20-30% of the applied insecticide remained in the sandy loam and 40-50%
in the peaty loam (Suett, 1971).

Carrots grown in soil treated at the rate of 2.0 kg active/ha contained
residues of 0.02-0.13 ppm at 14 weeks and 0.013-0.043 ppm at 26 weeks.

Chlorfenvinphos was applied to the surface of a pond at a rate that
gave an average concentration of 6.1 ppm. After 5 hours this had
decreased to 2.0 ppm and to 0.12 ppm after 1 month. Residues in mud
reached a maximum of 0.32 ppm 115 hours after treatment and persisted
for at least 34 days. The number of chironomidae larvae decreased
(Beynon et al., 1971).
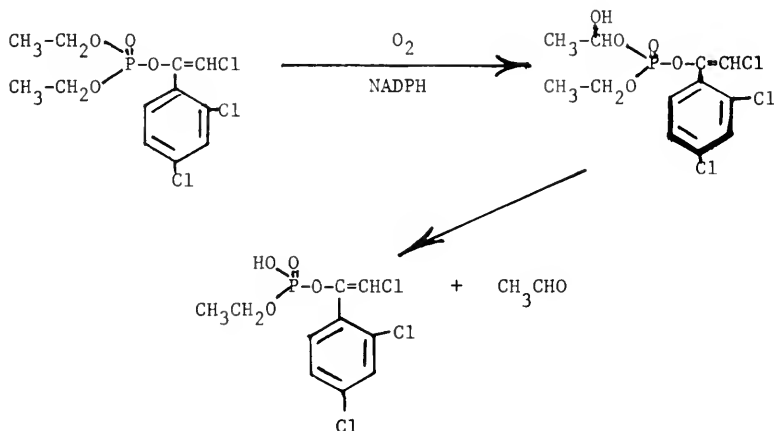
CHLOROBENZILATE [Ethyl-4,4'-diphenylglycollate]

CHLOROPROPYLATE [Propyl-4,4'-diphenylglycollate]

Benzilate acaricides were applied topically to soybean leaves.
Analyses of treated leaves revealed that the compounds were
quite stable and were translocated to other plant tissues to
a limited extent (Hassan and Knowles, 1969).

Chlorobenzilate was actively metabolized by liver fractions.
The major metabolites were dichlorobenzophenone and chloro-
benzoic acid. Dichlorobenzilic acid, dichlorobenzhydrol and
three unidentified compounds were also observed. CBA degraded
to three unknowns (Knowles and Ahmad, 1971).

Chloropropylate was metabolized by rat liver preparations.
Metabolites detected were qualitatively similar to those of
chlorobenzilate. The major metabolite was again DBP (Knowles
and Ahmad, 1971).

The yeast Rhodotorula gracilis metabolized chlorobenzilate and
chloropropylate to several compounds. Arising from these compounds,
were 4,4'-dichlorobenzilic acid and 4,4'-dichlorobenzophenone.
Using ^{14}C-chlorobenzilate or ^{14}C-chloropropylate labeled at the
carboxyl group, $^{14}CO_2$ was obtained. The major steps appear to be
hydrolysis followed by decarboxylation (Miyazaki et al., 1969 and
1970).

<u>CHLORONEB</u> [1,4-Dichloro-2,5-dimethoxybenzene]

Chloroneb was fed to rats, cows and dogs. In urine, the metabolite found was 2,5-dichloro-4-methoxyphenol in free and conjugated form probably as glucuronides and **sulfates.** This was not detected in hydrolyzed feces. No metabolites were found in the milk. After incubation of chloroneb with the 10,000 g supernate fraction of beef liver, the same metabolite was observed (Gutenmann and Lisk, 1969; Rhodes and Pease, 1971).

Snapbeans, grown in a greenhouse, were treated with C^{14} ring-labeled chloroneb. Analysis of plant tissues showed the presence of 2,5-dichloro-4-methoxyphenol, 2,5-dichlorohydroquinone and 2,5-dichloroquinone. In keyport silt loam in Delaware, chloroneb exhibited a half-life of 3 to 6 months when incorporated 2 to 3 inches below the surface. About 90% of the residue was unchanged chloroneb. The remainder was unidentified polar compounds. TLC-radioautography indicated that the unknown is not the phenol, hydroquinone or quinone (Rhodes et al., 1971).
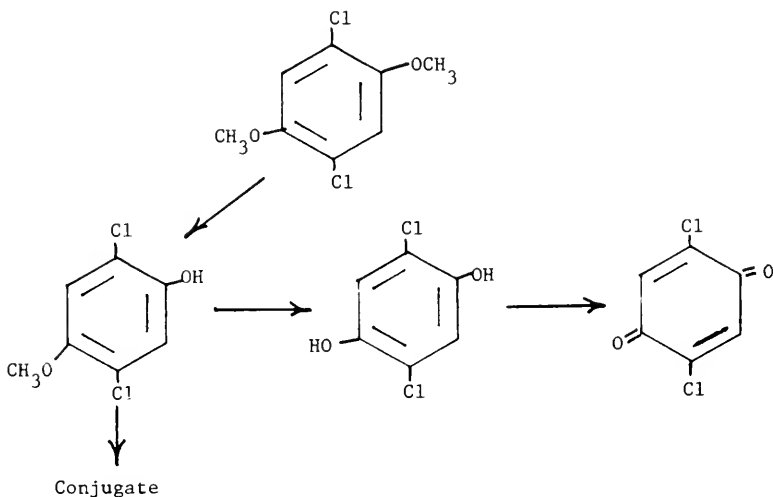
p-Chlorophenyl-N-methylcarbamate

A single oral dose of labeled p-chlorophenyl-N-methylcarbamate was given to rats and milking goats. $^{14}CO_2$ was expired after carbonyl-^{14}C but not after ring-labeled compound was administered. Most of the ring label was excreted in the urine; a trace, in the feces. Goat milk and rat and goat tissues contained traces of the radioactive carbon 48 hours after dosing. In the goat urine, p-chlorophenol (II) and its glucuronide (III), p-chlorophenyl sulfate (IV), 4-chlorocatechol-1-sulfate (V) and three minor unidentified metabolites were found. Goat milk contained compounds IV and V; and rat urine contained compounds II, III, and IV (Paulson et al., 1972).

Leghorn hens were given a single oral dose of ring or carbonyl ^{14}C-labeled p-chlorophenyl-N-methylcarbamate. When the carbonyl-labeled compound was administered, 69.5% of the ^{14}C-label was expired during the 48-hour collection period. None was detected when the ring-labeled compound was given. However, 95% of the label appeared in the urine after administration of the ring labeled compound. Urinary metabolites were identified as p-chlorophenyl sulfate and glucuronide, and p-chlorophenol. Feces also contained these metabolites, as well as the parent compound (Paulson and Zehr, 1971).
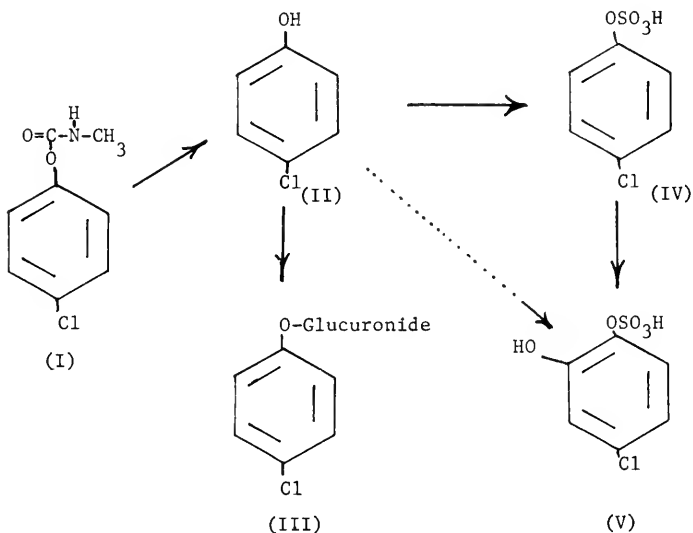
6-Chloro-2-trifluoromethylimidazo [4,5-b] pyridine (CTIP)

Rats metabolized the subject herbicide by hydroxylation at the 5-, 6-, or 7- positions. Conjugates of these metaboliates were found in the urine. In maize grown in treated soil, similar metabolites were found, free and conjugated. Using ^{14}C-labeling in the trifluoromethyl group, 25% of the label in 9-week-old maize was present as trifluoroacetic acid (Bond and Corbett, 1970).

As in rats, initial metabolism of CTIP in maize was by ring hydroxylation. This was followed by conjugation (Bond and Corbett, 1971).

Metabolic scheme: CTIP structure with labels — "Maize" → Conjugate; "Maize Rat", "Maize Rat", "Maize Rat" branches leading to hydroxylated/oxo structures; Cl?, HO- structure → Conjugates (Maize Rat); 6-oxo structure → Conjugates (Maize Rats) and [?] → CF₃-COOH; 7-oxo structure → Conjugates (Maize Rat).

CHLORPROPHAM (CIPC) [Isopropyl-N-(3-chlorophenyl) carbamate]
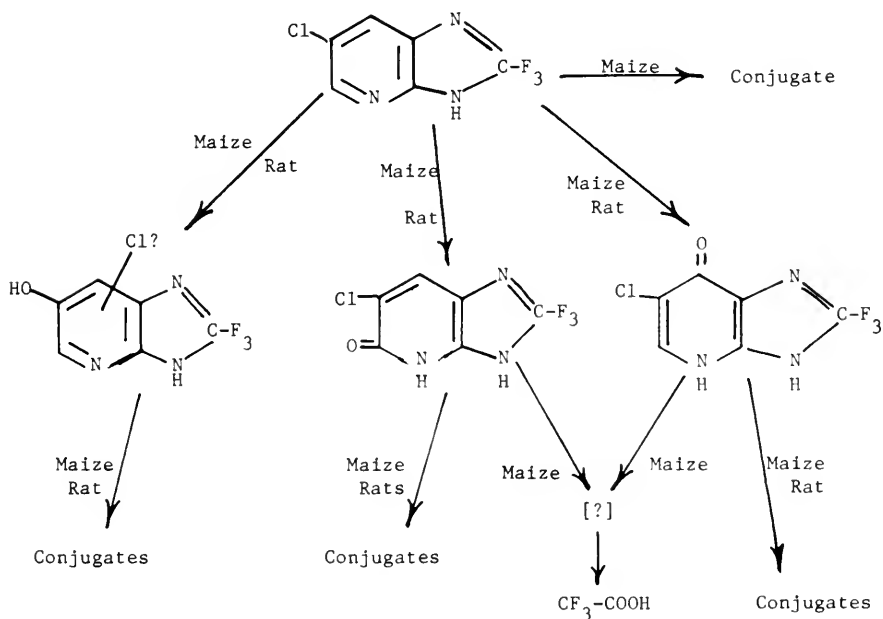
Following oral administration of chlorpropham to rats, renal excretion was followed. The most important metabolite was the p-hydroxy analog. Although the expected hydrolysis products were not found free, the N-acetyl hydroxyl analogs were excreted and identified. The 1-carbethoxy compound and a metabolite believed to be 1-hydroxypropyl-2-N-(3-chloro-4-hydroxyphenyl) carbamate was found but the latter has not yet been synthesized for confirmation of structure. Some chloraniline was excreted in the conjugated form. Compound II was conjugated as the sulfate and β-D-glucuronide (Grunow et al., 1970; Bobik et al., 1972).

Sub-lethal concentrations of labeled CIPC were applied to leaves or to roots of redroot pigweed (Amaranthus retroflexus L.), pale smartweed (Polygonum lapathiofolium L.) and parsnip (Pastinaca sativa L.). Water soluble metabolites, not identified, were extracted from all three species. The metabolites apparently were not the result of CIPC cleavage but probably conjugates with plant components. Very little $^{14}CO_2$ was released by any of the species in 3 days (Prendeville et al., 1968). In other studies, alkaline hydrolysis of the metabolites resulted in the formation of 3-chloroaniline. Hydrolysis also resulted after incubation with β-glucosidase. The aglycone was characterized as a modified CIPC molecule. The modification did not occur in the ring nor did it involve hydroxylation at the nitrogen atom (James and Prendeville, 1969). Studies with soybean plants gave similar results. Further studies to identify the aglycone suggested that the most likely biological alteration is hydroxyla-tion or oxidation of the phenyl ring (Still and Mansager, 1971).

After root treatment of soybean plants with CIPC, the polar metabolites of CIPC from root and shoot tissues were isolated and purified. After β-glucosidase hydrolysis and acetylation of the released aglycones, GLC-MS was used to identify the products. The data showed that the major root metabolite was 0-glucoside of 2-hydroxy CIPC. This was also found in shoots but in amall quantity. The major metabolites in shoot tissue were unidentified dechlorinated hydroxy-CIPC compounds and were not hydrolyzed by the β-glucosidase (Still and Mansager, 1972).

Arthrobacter sp. and Achromobacter sp. degraded chlorpropham with formation of the aniline (Clark and Wright, 1970b). In addition to the aniline and alkyl moieties, microbial degradation liberated CO_2 and chloride (Clark and Wright, 1970b).

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HN–C–O–CH–CH₃ with CH₃ ... Cl (Chlorpropham) (I)

(II) NH₂ ... Cl

(III) NH₂ ... Cl, OH

COOH, O–C–O–CH–CH₃ (VII) HN– ... Cl, OH

(V) HN–C–O–CH–CH₃ with CH₃ ... Cl, OH

CH₂OH, HN–C–O–CH–CH₃ ... Cl, OH (VI)

CH₂OH, H N–C–O–CH–CH₃ ... Cl, OH — as Sulfate

HN–C–O–CH–CH₂OH ... Cl, OH — as β-D-glucuronide

NH₂ ... Cl, HO (VIII)

HN–C–CH₃ ... Cl, OH (IV)

HN–C–CH₃ ... Cl, HO (IX)

NH₂ ... Cl, Glucoside–O (X)

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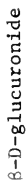
CHLORTHIAMID (Prefix) [2,6-Dichlorothiobenzamide]

DICHLOBENIL (Casoron) [2,6-Dichlorobenzonitrile]

BAM   [2,6-Dichlorobenzamide]

Kale plants, growing in pots, were subirrigated once with
solutions of chlorthiamid, dichlobenil, or BAM. The plants
exposed to BAM accumulated the parent compound and a glycoside
thought to be 3-hydroxy-2,6-dichlorobenzamide glycoside. When
dichlobenil was applied to soil surrounding 8-year-old apple
trees, the apple leaves accumulated dichlobenil, BAM, 2,6-
dichloro-3-(and 4-) hydroxybenzamide, 2,6-dichloro-3-(and 4-)
hydroxybenzonitriles, and some unidentified material (Verloop
and Nimmo, 1971).

Seedlings of Phaseolus vulgaris L. absorbed dichlobenil and
translocated it throughout the plant. In the leaves, part
evaporates and part is metabolized. Hydroxylation, followed by
conjugation, is the primary pathway. In addition to formation of
2,6-dichloro-3-(and 4-) hydroxybenzonitrile, some hydrolysis of
dichlobenil to 2,6-dichlorbenzamide and 2,6-dichlorobenzoic acid
also occurred. Glucosides of the hydroxy compounds were also
formed. The hydroxylated compounds were also seen in wheat and
rice seedlings. As in bean plants, these compounds were present
mainly as soluble (glucoside) and insoluble (polysaccharide)
conjugates. No evidence of hydrolysis of dichlobenil in wheat
and rice was obtained. In soil, the conversion of dichlobenil
to BAM was a microbiological process with $t_{1/2}$ = 1 1/2 to 12 months.
Similarly the hydrolysis of BAM was very slow. Some decarboxylation
of the hydrolysis product was observed (Verloop and Nimmo, 1969;
1970 a and b; Verloop and Daams, 1970).

Seedlings of wheat (Triticum vulgare) and rice (Oryza sativa) were
exposed to labeled dichlobenil by immersion of their roots in a
solution of the herbicide. Both plants absorbed the dichlobenil
from water solutions and translocated it to the shoots. In wheat,
dichlobenil was hydroxylated to the 3- and 4-hydroxy analogs and
converted to soluble and insoluble conjugates. The same processes
occur in rice but at a lower rate (Verloop and Nimmo, 1970a).

Bean seedlings (Phaseolus vulgaris) also absorbed and translocated
dichlobenil. The principal metabolic pathway was found to be
hydroxylation followed by conjugation. The 3- and 4-hydroxy analogs
were formed in a ratio of about 4:1. Hydrolysis of dichlobenil, not

observed in wheat and rice, occurred in bean seedlings to a very small extent and gave rise to 2,6-dichlorobenzamide and -benzoic acid (Verloop and Nimmo, 1969).

In sandy soil, dichlobenil underwent hydrolysis to the benzamide and three unidentified compounds. This breakdown is probably of a microbiological nature (Verloop and Nimmo, 1970b; Briggs, 1970).

[14]C-Dichlobenil was placed beneath the surface of soil surrounding an apple tree. Twenty weeks after application, about half the leaves on the tree showed leaf margin chlorosis. Analysis of leaves showed the presence of BAM, 2,6-dichloro-3-hydroxybenzamide, 2,6-dichloro-4-hydroxybenzamide, 2,6-dichlorohydroxybenzonitriles, unidentified material, and unchanged dichlobenil. After exposure of an apple tree to BAM, unchanged BAM, unidentified material, and 2,6-dichloro-3(and 4)-hydroxybenzamides were found in the leaves (Leach et al., 1971).

Kale plants (Brossica oleracea ssp. acephala) were exposed to BAM solutions by immersion of roots into a solution of the herbicide or through soil treatment. Leaf margin chlorosis developed quickly. With chlorthiamid and dichlobenil, the delay in appearance of symptoms was comparable to the half-life of dichlobenil in various soils.

Half-Life

Dosage	chlorthiamid	Dichlobenil	bAM
2.5mg/pot	46 days	44 days	5 days
0.5	>60	46	7
0.25	>60	46	9

In soil, the half-life of dichlobenil was 28 weeks at 6.7°C (after an initial 10 week lag period) and 19 weeks at 26.7°C. The decomposition activation energy was calculated as 3.57 k cal per mole. The only detectable metabolite was 2,6-dichlorobenzamide (Montgomery et al., 1972).

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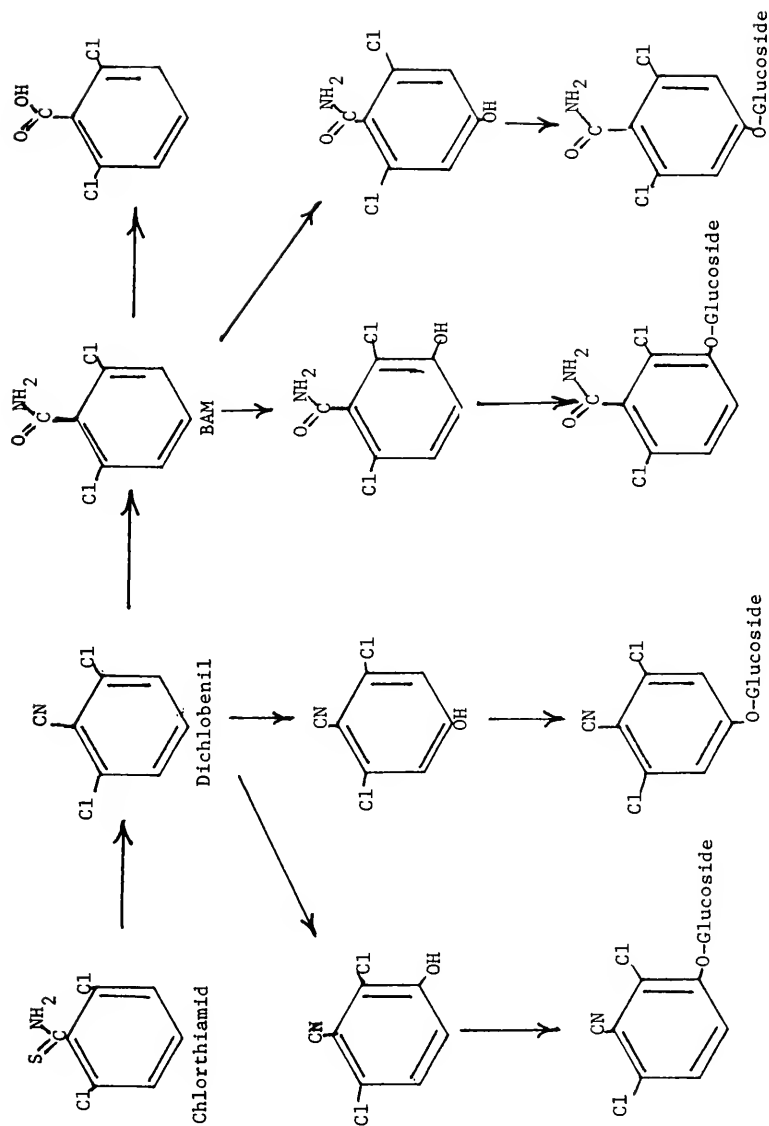
CIODRIN [αa-Methylbenzyl-3-(dimethyoxyphosphinyloxy)crotonate]

Degradation of ciodrin varied between soils. The half-life value
varied from 2 hours in a poygan silty clay loam to 71 hours in an
Ella loamy sand. In aqueous soil-free systems $t_{1/2}$ values for
ciodrin degradation were 180, 410, and 540 hours at pH 9,6, and
2, respectively (Konrad and Chesters, 1969).

COUMAPHOS (Coral, Muscatox, Bayer 21/199) [O,O-Diethyl-O-(3-chloro-
          4-methyl-2-oxo-1,2-benzopyran-7-yl)phosphorothioate]

Larvae of the cattle tick (Boophilus microplus) metabolized coumaphos
to the oxygen analog (Coroxon), diethyl phosphate, and diethyl
phosphorothioate (Roulston et al., 1969).

Coumarin [1,2-Benzopryone]

When labeled coumarin was fed to rabbits, 80% of the ^{14}C was excreted via urine within 24 hours. In addition to an acid-labile coumarin precursor (14.9%), all monohydroxycoumarins were observed: 3-hydroxy (21.7%); 4-hydroxy-(0.6%); 5-hydroxy-(0.4%); 6-hydroxy-(3.4%; 7-hydroxy-(12%); 8-hydroxy-(1.9%). In addition to these, o-hydroxyphenylacetic acid (20%) and o-hydroxyphenyllactic acid (3%) were also found. The hydroxycoumarins were excreted primarily as conjugates (Kaighen and Williams, 1961).

In the rat, about half the label was excreted via urine and half in feces. About 3% of the dose was excreted as hydroxycoumarins and 5% as an acid-labile coumarin precursor. Ring opening occured more extensively in rats than in rabbits and the main urinary metabolite in rats was o-hydroxyphenylacetic acid (20%). The precursor to this was probably 3-hydroxycoumarin (Kaighen and Williams, 1961).

Coumarin and 4-methylcoumarin were metabolized by rat-liver microsomes. The major metabolites of coumarin were identified as 3- and 7-hydroxycoumarin, o-hydroxyphenyllactic acid, and o-hydroxphenylacetic acid. Metabolites derived from 4-methylcoumarin showed chromatographic and spectral characteristics similar to metabolites of coumarin, suggesting that they are the methyl analogs of corresponding coumarin Metabolites (Gibbs et al., 1971).

Following injection of labeled coumarin into female albino Wistar rats, 80% of the dose was expired or excreted within 16 hours. In the collected urine, the following metabolites were identified: 5-hydroxycoumarin, 7-hydroxycoumarin, 8-hydroxycoumarin, o-coumaric acid, and melilotic acid. Another compound, labile in boiling acid, was not identified. Some o-hydroxyphenylacetic acid was also obtained. The 7-hydroxycoumarin was excreted free and conjugated. The presence of a small quantity of β-resorcylic acid in the urine after treatment of a rat with the 7-hydroxy analog indicated opening of the lactone ring and formation of 2,4-dihydroxycinnamic acid. By β-oxidation, this can then give rise to 2,4-dihydroxybenzoic acid. This also supports the finding that o-coumaric acid can be formed from coumarin (Van Sumere and Teuchy, 1971).

The hydroxylating enzyme system in rabbit liver microsomes, which hydroxylates position 7 of coumarin, was studied. The Michaelis constant for coumarin was 6.3 X 10-^{6}M. This hydroxylase was inhibited by CO. Diethyldithiocarbamate, KCN and EDTA were non-competitive inhibitors (Kritz and Stavdinger, 1965).

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o-Coumaric Acid
(o-Hydroxy-trans-
cinnamic acid)

o-Coumaryl glucoside

trans-Cinnamic acid

Melilotic Acid

o-Coumarinyl glucoside

Dihydrocoumarin

Coumarin

o-Coumarinic Acid
(o-Hydroxy-cis-cinnamic
acid)

113
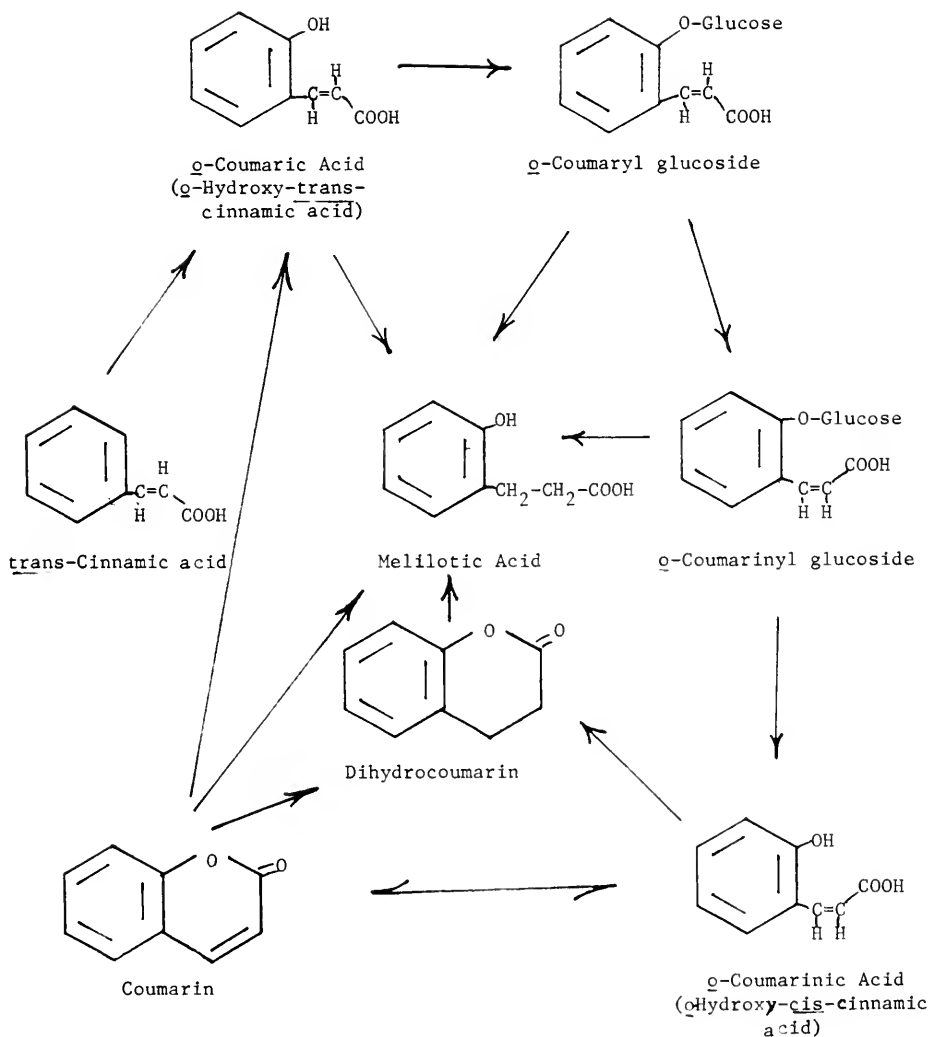
Anaerobic incubation of coumarin with extracts of rabbit or rat in-
testinal microflora yielded melilotic acid. The initial step involved
reduction to dihydrocoumarin and ring fission to melilotic acid. In
urine of rats, following oral administration of coumarin, o-coumaric
acid was observed in trace amounts. The most prominent metabolite in
urine was o-hydroxyphenylacetic acid (Scheline, 1968).

The mechanism of conversion of coumarin to melilotic acid was studied
with the fungus Taphrina wiesneri. These studies indicated a number
of different potential reaction routes (Fujii et al., 1971).

Main Route For Rabbits

Coumarin

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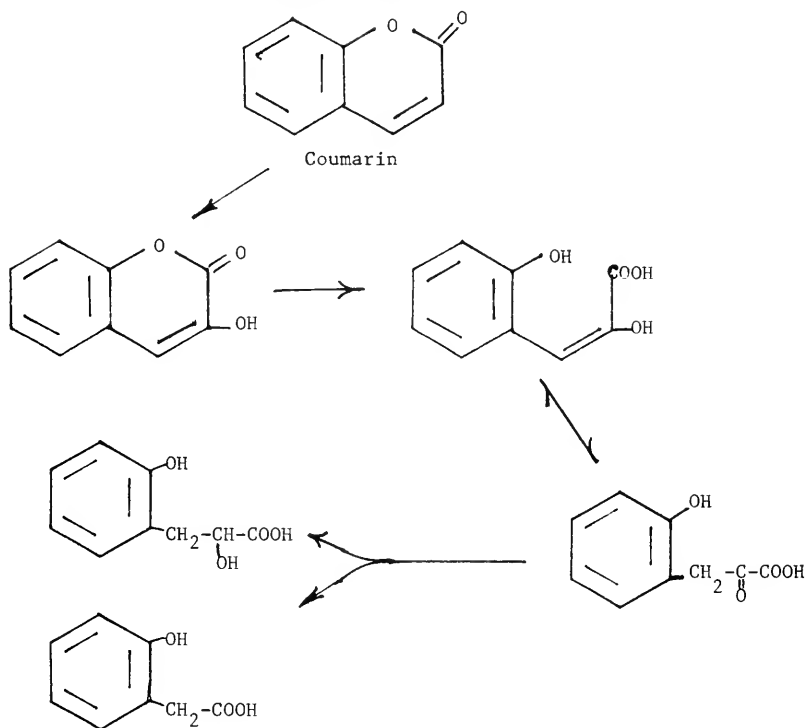
CYANIDE

In studies on microbial treatment of industrial wastes containing
cyanide, it was found that Fusarium solani induced a cyanide-
degrading enzyme system during the process of its adaption to
cyanide. No details of the reaction were given except that
ammonia production paralleled cyanide consumption (Shimizu et al.,
1969 a and b; 1970 a and b).

S-2-Cyanoethyl-N-[(methylcarbamoyl)oxy]thioacetimidate (Talcord, WL 21959, SD 17250)

When ingested by rats, this carbamate was rapidly metabolized and excreted. Tissue residues accounted for only a small proportion (less than 5%) of the total material ingested. About 40% of the dose appeared in the urine and 36% in exhaled air. The volatile metabolites were trapped and identified as CO_2 and acetonitrile. From collected urine, a metabolite was obtained and identified as S-2-cyanoethyl-N-hydroxythioacetimidate (II). The O-sulfate (III) and O-glucuronide(IV) were also observed. The same results were obtained when dogs were used (Hutson et al., 1971d).
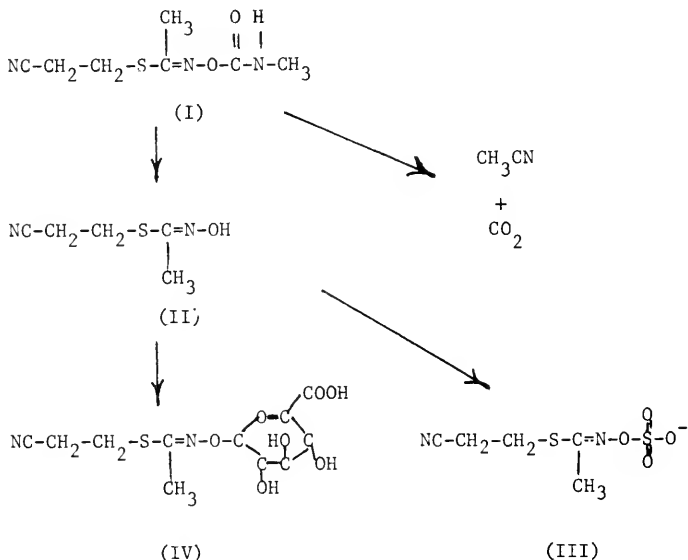
CYANOX [0,0-Dimethyl-0-(4-cyanophenyl) phosphorothioate]

Labeled cyanox was orally administered to male Wistar rats.
Absorption from the gastrointestinal tract occurred readily and
elimination was rapid and complete. Within 96 hours, 90% of the
label was excreted via urine and 10% in feces. $^{14}CO_2$ expiration
was neligible. Degradation products in the urine were identified
as demethylcyanox, demethylcyanoxon, p-cyanophenol and p-cyanophenyl-
sulfate (Wakimura and Miyamoto, 1971). In rabbits p-cyanophenol
was reported to be conjugated mainly with glucuronic acid
(Smith, 1949).

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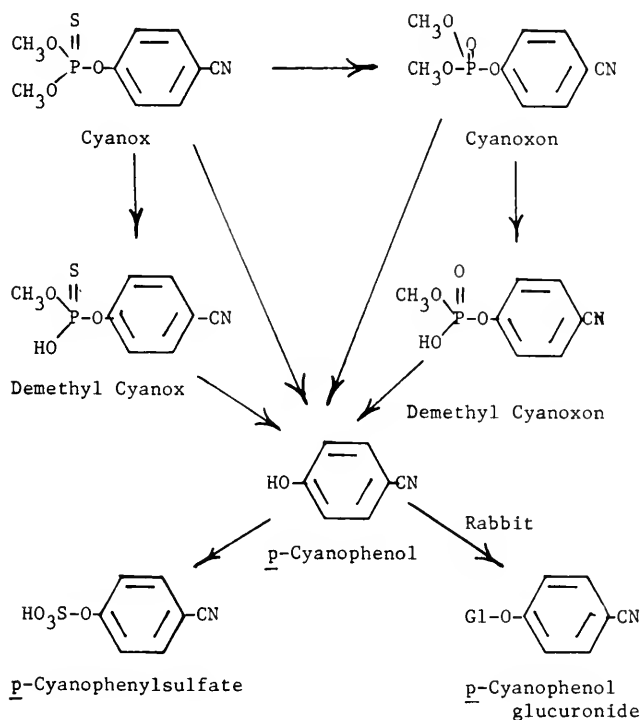
CYCLOHEXIMIDE [β-(2-(3,5-dimethyl-2-oxocyclohexyl)-2-hydroxyethyl) glutarimide]

After application to oranges, cycloheximide was found largely on the peel. Partial degradation occurred on the peel and gave rise to anhydrocycloheximide (Fisher, 1971).

CYCLOPHOSPHAMIDE (CP) [2-bis(2-chloroethylamino)-2-oxo-tetrahydro-2H-1,3,2-oxazaphosphorine]

Sheep were orally dosed with cyclophosphamide. In the collected urine, two metabolites were observed and characterized as O-(2-carboxyethyl)N,N-bis (2-chloroethyl)phosphorodiamidate (VI) and 2-[bis (2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazophosphorine 2,4-dioxide (II) (4-ketocyclophosphamide)(Bakke et al., 1971).

In other studies, in the urine of sheep given single oral doses of labeled CP(I), eight metabolites were observed and were either identified (unchanged CP, compounds II, III and VIII) or characterized by mass spectrometry (compounds IV, V, VI, and VIII) (Bakke et al., 1972).

From the urine of a dog intravenously administered cyclophosphanide, a compound was isolated and identified by mass spectral and infrared analyses and synthesis as 4-ketocyclophosphamide (II) (Hill et al., 1970). Compound VI was also observed (Struck, 1971).

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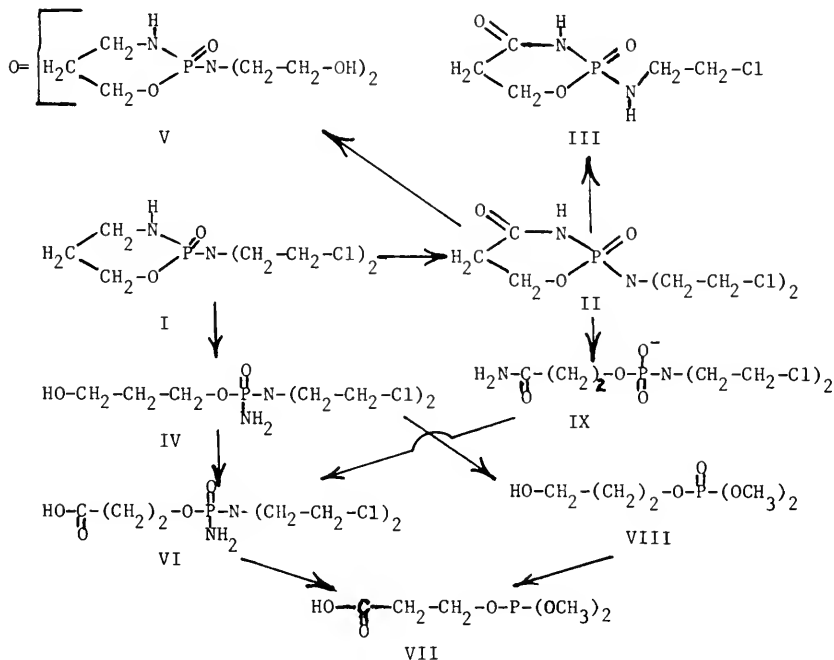
2,4-D and RELATED COMPOUNDS

<u>2,4-D</u>   [2,4-Dichlorophenoxyacetic Acid]

<u>2,4-DB</u> [4-(2,4-Dichlorophenoxy)butyric Acid]

<u>Erbon</u> [2-(2,4,5-Trichlorophenoxy)ethyl 2,2-dichloropropionate]

<u>MCPA</u>   [4-Chloro-2-methylphenoxyacetic Acid]

<u>Silvex</u> [2-(2,4,5-Trichlorophenoxy)propionic Acid]

<u>2,4,5-T</u>[2,4,5-Trichlorophenoxyacetic Acid]

<u>CPA</u>   [Chlorophenoxyacetic Acid]

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2,4-D [2,4-Dichlorophenoxyacetic Acid]

After application of 2,4-D methyl ester to alfalfa, in addition to an unknown compound, the butyric and caproic analogs were observed. This study suggested that alfalfa was capable of lengthening the aliphatic chain of 2,4-D. Similar results were obtained with 2,4-DB, 4-(2,4-dichlorophenoxy)crotonic acid, and 4-(2,4-dichloro-phenoxy)-β-hydroxy)butyric acid (Linscott and Hagin, 1970).

Studies with 2,4-D as an inducer of plant callus showed that 2,4-D formed complexes with proteins. 2,4-D formed complexes with lysine-rich histones at an early stage of callus induction (Yasuda and Yamada, 1970).

From resistant grasses such as bromegrass (Bromus inermis Leyss.), timothy (Phleum pratense L.), and orchardgrass (Dactylis glomerata L.), a new metabolite was identified after gas chromatography and mass spectroscopy as 3-(2,4-dichlorophenoxy)propionic acid [3-(2,4-DP)] (Hagin et al., 1970). In the resistant plants burcucumber (Sicyos angulatus L.) and oats (Avena sativa L.), 2,4-D was immobilized in the treated leaves. In susceptible cocklebur (Xanthium sp.), it remained largely as free and mobile 2,4-D (Dexter et al., 1971).

Bean, bluegrass, and corn were exposed to 2,4-D. Chromatographic analyses indicated that all three plants metabolized 2,4-D. The major metabolite appeared to be the 4-hydroxy-2,5-dichlorophenoxy-acetic acid (4-OH-2,5-D) and the minor metabolite appeared to be 4-hydroxy-2,3-dichlorophenoxyacetic acid (4-OH-2,3-D). Essentially all 2,4-D absorbed by bluegrass or corn was rapidly conjugated. This reaction was slower in beans. Some side chain oxidation also occurred (Montgomery et al., 1971).

Hydroxylation of 2,4-D varied qualitatively and quantitatively. Wild buckwheat (Polygonum convolvulus L.), leafy spurge (Euphorbia esula L.), yellow foxtail (Setaria glauca L.) and wild oat (Avena fatua L.) hydroxylated 2 to 7% of absorbed 2,4-D in a seven day period. Only traces of hydroxylation products were observed in wild mustard [Brassica kaber (DC.) L.C. Wheeler var. pinnatifida (Stokes) L.C. Wheeler], perennial sowthistle (Sonchus arvensis L.) and Kochia (Kochia scoparia L. Roth). The hydroxylation product 4-hydroxy-2,5-dichlorophenoxyacetic acid (4-OH-2,5-D) was detected, in varying amounts, in all these weed species. The 4-hydroxy-2,3-dichlorophenoxyacetate (4-OH-2,3-D) was detected in wild buckwheat, wild oat, and yellow foxtail only. 2-Chloro-4-hydroxyphenoxy-acetic acid (4-OH-2-CPA) was found in the three foregoing species and leafy spurge (Fleeker and Steen, 1971).
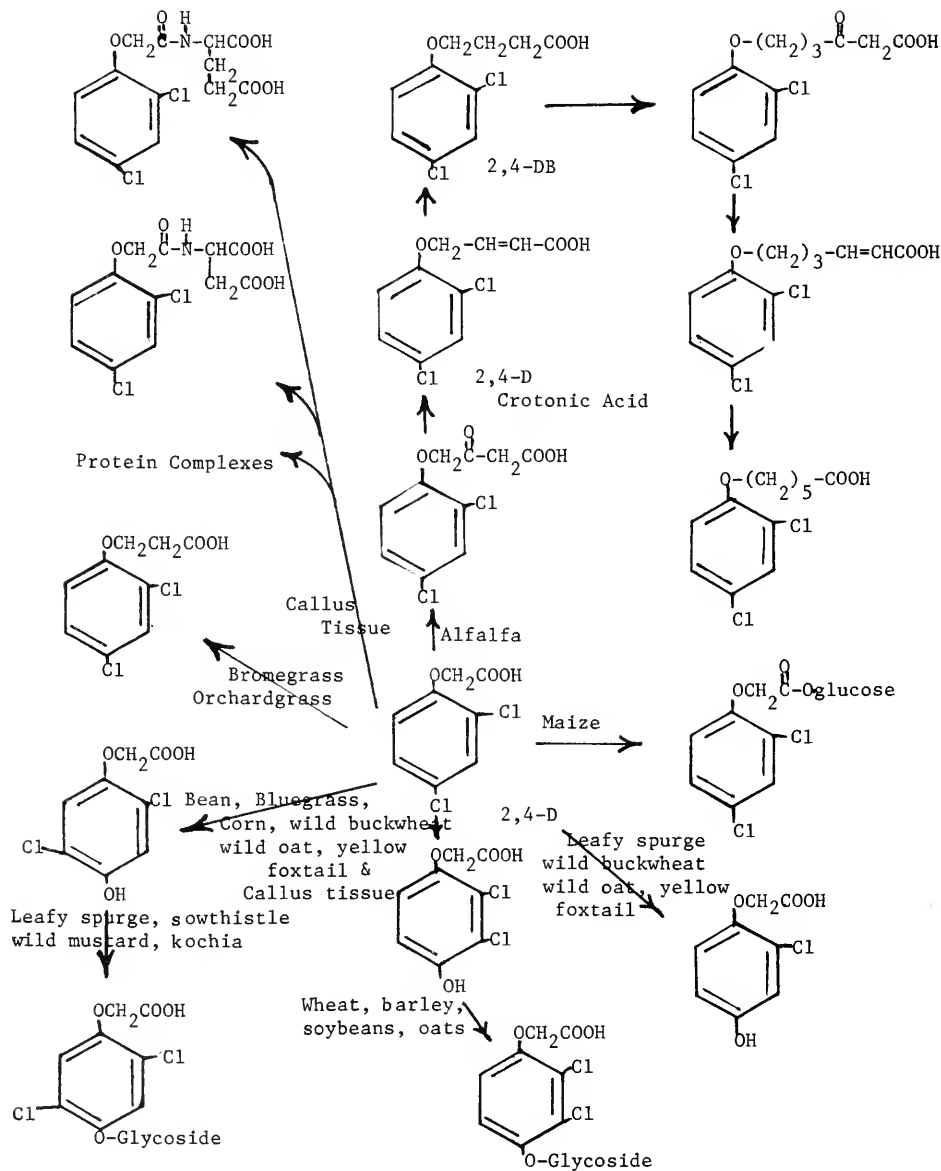
After application of 2,4-D, the major water soluble metabolites in soybean callus tissue were glycosides of ring hydroxylated 2,4-D. In addition to the glycoside of 4-OH-2,5-D, the glycoside of 4-OH-2,3-D and two unidentified compounds were also detected after emulsin treatment. One ether soluble metabolite was identified as a 2,4-D conjugate of glutamic acid and another as the 2,4-D aspartate. Other ether soluble metabolites of 2,4-D were not identified (Chkanikov et al., 1972; Feung et al., 1971 and 1972). In the bean plant itself, the major metabolite 4-OH-2,5-D and a minor metabolite 4-OH-2,3-D were present as glycosides as well as the free aglycones. Preliminary experiments indicated that these metabolites are formed in wheat, barley, soybeans, and oats (Hamilton et al., 1971).

In maize plants, one of the water-soluble metabolites was identified as a glucose ester of 2,4-D. In bean plants, the water-soluble metabolites of 2,4-D were mainly glucosides of hydroxylated 2,4-D. The presence in maize of some 2,4-D as glucosides of hydroxylated 2,4-D was also indicated (Chkanikov et al., 1971).

Cultures of Pseudomonas N.C.I.B. 9340 were grown in the presence of 2,4-D. From these were isolated materials identified as 2,4-dichloro-phenol, 3,5-dichlorocatechol and 6-OH-2,4-D. Incubation of 3,5-dichloro-catechol with a cell-free extract produced a ring-fission product pro-visionally identified as α,γ-dichloromuconic acid. This in turn gave rise to γ-carboxymethylene-α-chloro-$\Delta^{\alpha,\beta}$-butenolide. Enzymic hydrolysis then gave rise to a compound whose proposed identity was α-chloro-maleylacetate, (Evans et al., 1971a).

Pseudomonas N.C.I.B. 9340 also grew without lag on 2-chlorophenol and 3-chlorocatechol. Using cell-free extracts, α-chloromuconate was isolated as the product of ring fission (Evans et al., 1971a),

Enzyme preparations were obtained from an Arthrobacter sp. grown on 2,4-D. When the enzyme preparation was incubated with catechol, 3-methyl-, 4-methyl-, 4-chloro-, or 3,5-dichlorocatechol, UV absorp-tion measurements indicated a conversion to the corresponding muconic acids. Isolation, UV, IR, and chromatography confirmed these trans-formations. Incubation of biologically accumulated cis,cis-3-chloromuconic acid with the enzyme yielded a product with λ_{max} 242mμ, probably the chlorobutenolide. This in turn, yielded the corresponding maleylacetic acid. Similarly, incubation of 3,5-dichlorocatechol, cis,cis-dichloromuconic acid or the chlorobutenolide with the enzyme also yielded a product with λ_{max}= 253mμ, identical with that for synthetic chloromaleylacetic acid. At the end of the incubation period, all of the original radioactivity introduced as 2,4-D remained in the

aqueous phase. Chromatography indicated the product as succinic acid (Tiedje et al., 1969). In separate studies, the conversion of chloromaleylacetic acid and maleylacetic acid to succinic acid by Arthrobacter sp. enzymes was also observed (Duxbury et al., 1970).

In other studies with a soluble enzyme preparation from a soil Arthrobacter sp., the ether linkage was cleaved to yield 2,4-dichlorophenol, alanine and CO_2. Alanine and CO_2 probably arise subsequent to the condensation of glyoxylated or glycine (Tiedje and Alexander, 1969).

In studies with Neurospora crossa and Aspergillus niger, protocatechurate was metabolized to 3-oxoadipate (Thatcher and Cain, 1970).

Hydrolysis of isopropyl, n-butyl and iso-octyl esters of 2,4-D to the free acid was studied. In 0.1N - NaOH, hydrolysis was almost instantaneous for the three esters. In 0.1N - Na_2CO_3, hydrolysis was slower. In distilled water, over 90% of the esters was recovered unchanged after 5 hours. When added to soils, these esters also underwent hydrolysis to the free acid. After 24 hours, no isopropyl or n-butyl ester residues could be detected and only 20-30% of the iso-octyl ester remained. After 48 hours, only 10% of the octyl ester remained (Smith, 1972b).

2,5-Dichlorophenol has been detected in the defensive froth emitted by the grasshopper (Romalea microptera). Froth from Romalea collected at a biological station, on wild acreage where no herbicide or other chemical had been applied, lacked the 2,5-dichlorophenol (Eisner et al., 1971).
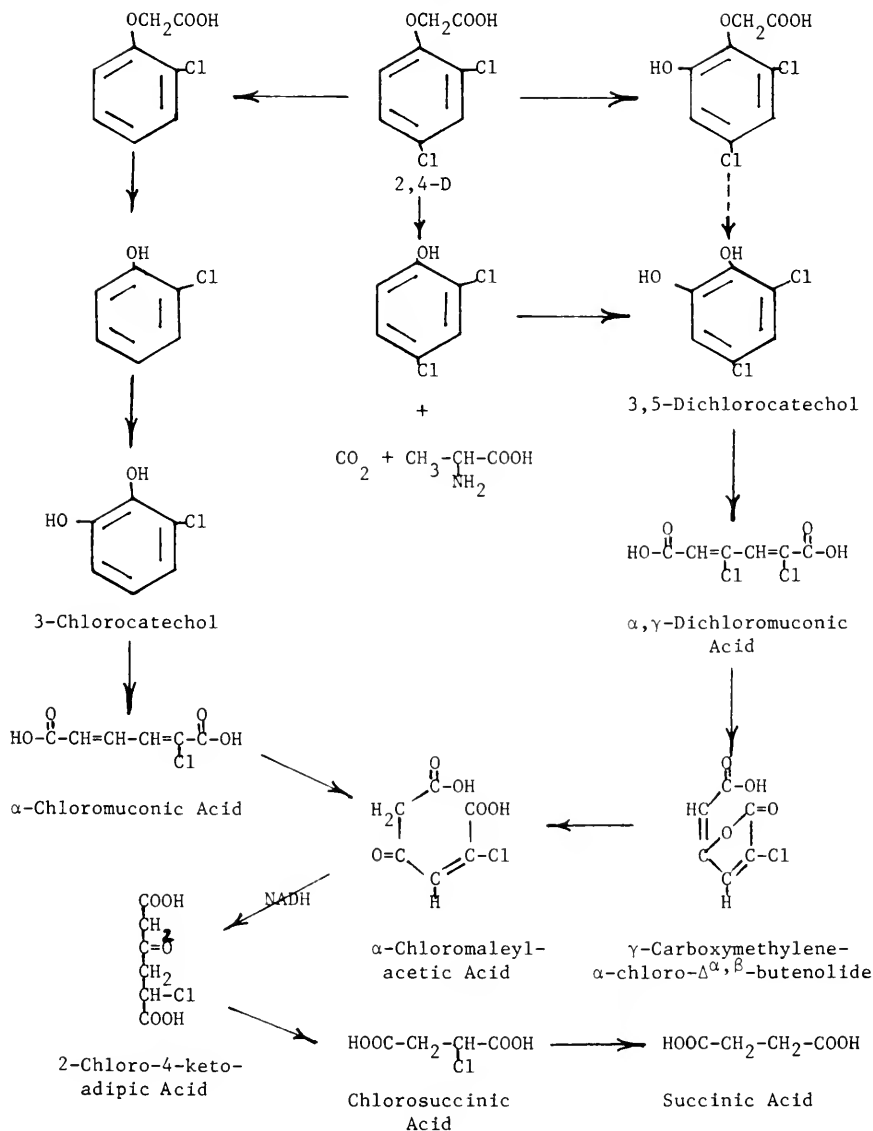
<u>2,4-DB</u> [4-(2,4-Dichlorophenoxy)butyric Acid]

Soybean (<u>Glycine</u> <u>max</u> L.) and cocklebur (<u>Xanthium</u> <u>sp</u>.) plants were treated with 2,4-DB. More metabolites were observed in chromatographed extracts of soybean than of cocklebur. The major metabolite was 2,4-D and an intermediate with an R_f similar to 4-(2,4-dichlorophenoxy)crotonic acid was observed in both plants. Another product was observed with an R_f similar to that of 10-(2,4-dichlorophenoxy)decanoic acid (Wathana and Corbin, 1972).

Esters of 2,4-DB, the crotonic acid analog, and the β-hydroxybutyric acid analog were applied to Saranac alfalfa at rates equivalent to 0.5 kg/ha of 2,4-D. After application of the ethyl ester of the β-hydroxy compound, 2,4-DB and the crotonic acid analog were found. After application of the crotonic methyl ester analog, 2,4-DB and the caproic acid analog were found. After 2,4-DB application, 2,4-D and the caproic acid were found (Linscott and Hagin, 1970).

<u>ERBON</u>   [2-(2,4,5-Trichlorophenoxy)ethyl 2,2-dichloropropionate]

After sheep were orally dosed with erbon, urine and feces were collected. Erbon was metabolized rapidly to 2,4,5-trichlorophenol and to 2-(2,4,5-trichlorophenoxy)ethanol. Peak concentrations were observed within the first 23 hours. Less than 2% of the total administered dose appeared in the feces; almost 60%, in the urine. Within 25 hours, metabolites had practically disappeared from the blood. Erbon was rapidly hydrolyzed when incubated with a liver homogenate or fresh rumen fluid and in urine, feces and blood. Only the ethanol compound was observed (Wright et al., 1969 and 1970).
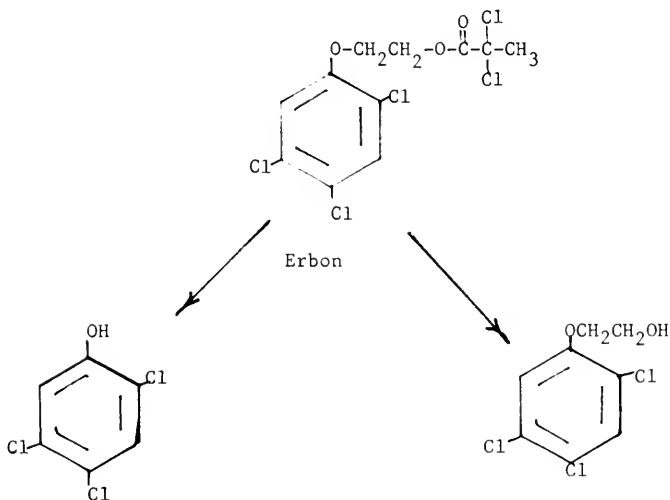
<u>MCPA</u> [4-Chloro-2-methylphenoxyacetic Acid]

In peas, rape (<u>Brassica</u> <u>napus</u>) and red campion (<u>Melandrium</u> <u>rubrum</u>),
two ether soluble metabolites were identified as 4-chloro-2-hydroxy-6-
methylphenoxyacetate and N-(MCPA)-aspartate. Another metabolite was
detected but not identified. A β-glycoside of hydroxy-MCPA was
detected in all species. In rape, 4-chloro-2-methylphenoxyacetyl-
β-D-glucose was tentatively identified. Another β-glycoside was
detected in peas (Collins and Gaunt, 1970 and 1971).

A pseudomonad, capable of utilizing MCPA as the sole carbon source,
was isolated from soil. Induction patterns suggested that 5-chloro-
<u>o</u>-cresol and 5-chloro-3-methylcatechol are intermediates in the
metabolism of MCPA. The **γ-ca**rboxymethylene-$\Delta^{\alpha,\beta}$-butenolide and
γ-hydroxy-α-methylmuconate were also tentatively identified. By
chromatographic, physical and chemical means, other detected culture
components have been identified: 4-chloro-6-hydroxy-2-methylphenoxy-
acetate, oxalate, γ-chloro-α-methylmuconic acid, and <u>o</u>- or <u>m</u>-cresol.
2-Methylphenoxyacetate was also detected but may have been an impurity
in the MCPA. With cleavage of the ether linkage, 5-chloro-<u>o</u>-cresol
and glyoxylate were formed. The latter could yield the observed
oxalate (Gaunt and Evans, 1971a,b; Gamar and Gaunt, 1971).

SILVEX (2,4,5-TP, Fenoprop) [2-(2,4,5-Trichlorophenoxy)propionic Acid]

The propylene glycol butyl ether ester of silvex (2,4,5-TP PGBE) was applied to the surface of three ponds at the rate of 9 kg/ha. Samples were collected and analyzed. The hydrolysis rate followed first order kinetics. Fifty percent hydrolysis of the ester occurred within 5-8 hours; 90%, in 16-24 hours; and 99%, in 33 to 49 hours. Adsorption of both the ester and acid appeared to occur in the sediment. Under laboratory conditions, silvex adsorption by the sediments conformed to the Freundlich adsorption equation. The pH of sediment from the three ponds was similar: 6.25, 6.09, and 6.07.

$$- \frac{dc}{dt} = kc$$

$$\log C - \log C_O = - \frac{kt}{2.303}$$

$$k = \frac{2.303}{t} \log \frac{C_O}{C}$$

The specific reaction rate constant (k, hr^{-1}) for the three ponds was calculated: 0.14, 0.10, 0.09 (Bailey et al., 1970).

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<u>2,4,5-T</u> [2,4,5-Trichlorophenoxyacetic Acid]

After a single oral dose of 50 mg/kg to a rat, urine was collected for
seven days. In addition to the free acid, 2,4,5-T was excreted in
conjugated form. One conjugate was isolated and identified as N-(2,4,5-
trichlorophenoxyacetyl)glycine (Grunow et al., 1971).

The metabolism of 2,4,5-T, after stem injection of pinto bean plants,
indicated that chlorine was eliminated from the 4-position and
4-OH-2,5-D was formed (Hamilton et al., 1971).

The microorganism <u>Brevibacterium</u> sp. was capable of cometabolism of
2,4,5-T. Chlorine was released as inorganic chloride. Another
material observed exhibited R_f values in three systems similar to
that of 3,5-dichlorocatechol (Horvath, 1971).

The major product of photodecomposition of 2,4,5-T was 2,4,5-trichloro-
phenol. The latter gave rise to 4,6-dichlororesorcinol, 4-chlororesor-
cinol and 2,5-dichlorophenol. Two other compounds were identified as
2-hydroxy-4,5-dichlorophenoxyacetic acid and 2,4,5-trichloroanisole
(Crosby and Wong, 1971).

CHLOROPHENOXYACETIC ACIDS

2-CPA [2-Chlorophenoxyacetic acid]

An aqueous solution of the sodium salt was irradiated with UV. After methylation and GLC, the 2-methoxyphenoxyacetate ester was identified. An acidic polymer and a compound exhibiting the same retention time as methylphenoxyacetate were also observed (Crosby and Leitis, 1969).

3-CPA [3-Chlorophenoxyacetic acid]

UV irradiation of an aqueous solution of the sodium salt gave rise to major compounds. One was identified as benzaldehyde. The other, as benzyl alcohol. 3-Methoxyphenoxyacetate was formed in small amounts. It was also observed that 3-hydroxphenoxyacetic acid was formed but was in turn converted to polymeric humic acids (Crosby and Leitis, 1969).

4-CPA [4-Chlorophenoxyacetic acid]

A pseudomonas, capable of utilizing 4-CPA as a sole carbon source, was isolated from soil. The following compounds were identified in culture extracts: 4-chloro-2-hydroxyphenoxyacetate, 4-chloro-catechol, β-chloromuconate, and γ-carboxyethylene-$\Delta^{\alpha,\beta}$-butenolide. It was found that β-chloromuconolactone was unstable in aqueous solution and hydrolyzed easily to the corresponding β-hydroxy analog (Evans et al., 1971b).

UV irradiation of sodium 4-chlorophenoxyacetate gave results parallel to those with the 3-isomer. Benzaldehyde, benzyl alcohol, phenylacetic acid and 4-hydroxyphenoxyacetic acid (Crosby and Leitis, 1969).

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<u>DACTHAL</u> (DCPA) [Dimethyl 2,3,5,6-tetrachloroterephthalate]

Two degradation products of DCPA were observed in soil, probably the result of microorganism activity: methyl 2,3,5,6-tetrachloroterephthalate and the free acid (Tweedy et al., 1968).

<u>Daxtron</u> [4-Hydroxy-2,3,5-trichloropyridine]

When incubated with fertile garden soils, Daxtron persisted for more than 275 days under aerobic and anaerobic conditions (Naik et al., 1972).

<u>D D</u> [Mixture of: 1,2-Dichloropropane and <u>cis</u>- and <u>trans</u>-
1,3-dichloropropenes]

Each of the components was individually fed to male and female
adult Carworth Farm E strain rats. Urine and feces were collected
and analyzed. Excretion of the administered materials was rapid
and 80-90% of the label used was eliminated during the first
24 hours of the experiment. Urine was the major route of
excretion of the administered dose: 50.2% 1,2-dichloropropane,
80.7% <u>cis</u>-1,3-dichloropropene, and <u>trans</u>-1,3-dichloropropene.
19.3% of the administered 1,2-dichloropropane was excreted as
CO_2. The <u>cis</u>-1,3-dichloropropene yielded only 3.9% CO_2 while
the trans isomer yielded 23.6% (Hutson et al., 1971).

Soil-water cultures converted dichloropropene to 3-chloroallyl
alcohol. Further studies with a pseudomonad indicated that the
<u>trans</u>-3-chloroallyl alcohol was converted to the <u>trans</u>-3-
chloroacrylic acid and then to formylacetic acid. The latter is
then decarboxylated (Belser and Castro, 1971).

DDT and RELATED COMPOUNDS

DDT [2,2-Bis(p-chlorophenyl)-1,1,1-trichloroethane]

$$\left(Cl-\langle\bigcirc\rangle\right)_2 -CH-C-Cl_3$$
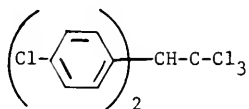
DDD (TDE, Rhothane) [2,2-Bis(p-chlorophenyl)-1,1-dichloroethane]

$$\left(Cl-\langle\bigcirc\rangle\right)_2 -CH-CH-Cl_2$$
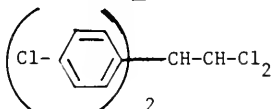
Kelthane (Dicofol) [2,2-Bis(p-chlorophenyl)-1,1,1-trichloroethanol]

$$\left(Cl-\langle\bigcirc\rangle\right)_2 \overset{OH}{\underset{}{-C-C-Cl_3}}$$
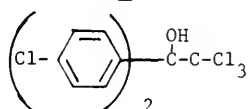
DDE [2,2-Bis(p-chlorophenyl)-1,1-dichloroethylene]

$$\left(Cl-\langle\bigcirc\rangle\right)_2 -C=C-Cl_2$$

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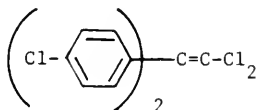
After ingestion of DDT or DDD by adult volunteers, DDA was excreted in urine. No increase in DDA excretion was observed after ingestion of DDE. DDD readily degrades further through a series of intermediates to DDA and is rarely found as a stored metabolite in the general population. DDE apparently does not undergo further break down to DDA; and this stability accounts in large part for the higher human tissue storage of DDE than of DDT in the general population (Morgan and Roan, 1971; Roan et al., 1971).

In recent studies, the question of conversion of o,p'-DDT to p,p'-DDT has been re-investigated. The results of these experiments indicated that this conversion did not occur in rats, sheep, chickens and quail (Cranmer, 1972; Bitman et al., 1971a,b).

Three groups of three cows each were fed p,p'-isomers of DDT, DDD, or DDE at the rate of 25 mg per day for 60 days. Equilibrium was not reached. When feeding of these compounds ceased, the decline in milk fat concentrations of all three materials could be described as the sum of two first order equations (Fries et al., 1969).

Sheep were orally dosed for 28 consecutive days with DDT, DDE and DDD individually. Maximum concentrations in fat were DDE > DDD > DDT (10:2:1, respectively). Rates of elimination were DDD > DDT > DDE (half-life=4,9 & 14 weeks, respectively). DDE appeared as a metabolite of DDD and DDT in fat. DDD appeared a metabolite of DDT. The correlation between DDE in fat and whole blood was expressed by the equation: $x = 1.8y -1.1$. Highest concentrations of DDT and DDE occurred in blood 15 hours and 32 hours respectively after dosing. DDD showed two maxima - at 8 hours and 32 hours after dosing (Hunnego et al., 1971).

Labeled DDT was administered i.p. to a gravid mouse. The same level of radioactivity was found in fetal and maternal blood. Residues of DDT and its metabolites (DDE, DDD, DCB, DDOH and DDA) were found in both maternal and fetal blood, brain, liver and fat (Schmidt and Dedek, 1972; Dedek and Schmidt, 1972.

p,p'-DDT was fed to rats for seven days. During this period rats were sacrificed on the first, second, fifth and seventh days. Analyses showed that DDD was localized in the liver; that DDT and DDA were nearly equally distributed in all organs. With the help of thin-layer chromatography, DCB, DDOH, and DDE were also found (Seidler et al., 1970). In other studies, two paths of metabolism were indicated. After intraperitoneal injection of DDE, DDMU,

DDNU, DDOH and DDA were observed. DDMS was not observed. Since this compound is indicated as intermediate between DDMU and DDNU in the conversion of DDT via DDD to DDA, it would appear that two paths are operative in the rat (Datta, 1970). Using isolated rat livers, it was found that the liver was capable of detoxifying DDT, DDE, DDD, DDMU, and DDMS. Isolated kidneys were able to detoxify DDMS, DDNU, and DDOH (Datta and Nelson, 1970).

An aldehyde has been proposed as the intermediate between DDOH and DDA. Preliminary studies indicated this intermediate to be very unstable. DDOH was incubated with liver alcohol dehydrogenase and then p-nitrophenylhydrazine was added. From the mixture was obtained a hydrazone which, when chromatographed in two different solvent systems, exhibited the same R_f values as an authentic p-nitrophenylhydrazone derivative of DDCHO. Mass spectrometry confined the identity of the compound as the aldehyde (Suggs et al., 1970).

In studies with rat brain tissue, the amount of DDT binding exceeded that of DDE only in the fraction containing the nerve endings. A sub-fraction containing mainly pre- and post-synaptic complexes had the highest DDT affinity. DDE had a higher affinity for soluble components than did DDT (Brunnert and Matsumura, 1969).

The in vitro reductive dechlorination of DDT by liver was investigated. Heated liver, to which riboflavin and an NADPH-generating system were added, was incubated with p,p'-DDT. Omission of either riboflavin or the NADPH-generating system almost completely inhibited the conversion of DDT to DDD. In the presence of both, conversion was 100%. This was also shown to be a linear function of riboflavin over a 2 hour period and within the range 5-50 ug riboflavin/1.5ml incubation mixtures (Hassal and Forrest, 1972).

The metabolism of o,p'-DDT in rats was studied after a single oral dose (Feil et al., 1971 and 1972). In more recent studies after a single oral dose, thirteen metabolites were identified: (1) 3-hydroxy-2,4'-DDT; (2) 4-hydroxy-3-methoxy-2,4'-DDT; (3) o,p'-DDD; (4) 3-methoxy-2,4'-DDD; (5) 4-hydroxy-3-methoxy-2,4'-DDD; (6) o,p'-DDA; (7) o,p'-DDA glycine conjugate; (8) o,p'-DDA aerine conjugate; (9) 3-hydroxy-2,4'-DDA; (10) 4-hydroxy-2,4'-DDA; (11) 5-hydroxy-2,4'-DDA; (12) 4-hydroxy-3-methoxy-2,4'-DDA; (13) o,p'-dichlorobenzhydrol. All compounds were found in feces. Although chromatography indicated the presence of several metabolites, only compound 13 (o,p'-dichlorobenzhydrol) was obtained in sufficient purity for identification purposes (Feil et al., 1973).

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5-HO-2,4'-DDA

3-HO-2,4'DDT

4-HO-3-CH$_3$O-2,4'-DDT

4-HO-2,4'-DDA

o,p'-DDT

3-HO-2,4'-DDA

o,p'-DDA

o,p'-DDD

3-HO-2,4'-DDD

4-HO-3-CH$_3$O-2,4'-DDA

4-HO-3-CH$_3$O-2,4'-DDD

o,p'-DBH

In other studies with microsomes from pigeon liver, the reduction of DDT to DDD proceeded rapidly under N_2, in the presence of NADPH, but stopped under aerobic conditions or showed lower activity in the presence of CO (Walker, 1969). The reduction of o,p'-DDT to o,p'DDD has been found to occur in tissues of dead birds (French and Jeffries, 1969). In addition to p,p'-DDT, pigeon liver preparations also reductively dechlorinated o,p'-DDT, p,p'-DDD, perthane, methoxychlor, and the pmethylphenyl and p-bromophenyl analogs of DDT (Hassal and Manning, 1972).

^{14}C-DDT was incubated with HeLA S cells. This was then extracted with hexane and developed by two-dimensional TLC. After autoradiography, DDE, DDD, DBP, and DBM were identified in addition to DDT and an unknown material near the origin (Huang et al., 1970).

Goldfish fed DDT stored about 40$ of it as DDT, DDD and DDE. Residue half-life values for tissues averaged 29 days (Grzenda et al., 1970); Young et al., 1971). In the dogfish, Squalus acanthias, p,p'-DDT was accumulated and stored in the liver (Dvorchik and Maren, 1972).

The marine diatom, Cylindrotheca closterium, concentrated DDT. The only metabolite detected was DDE (Keil and Priester, 1969). Fresh-water diatoms (Nitzschia sq. and an unidentified species) metabolized DDT to DDE only in small amounts (Miyazaki and Thorsteinson, 1972). Marine phytoplankton concentrated DDT to levels many times higher than the original concentrated of the medium. Small amounts of DDT were converted to DDE. In one culture, Skeletonema also produced a small amount of an unknown polar metabolite from DDT (Rice and Sikka, 1972). Ability of marine phytoplankton to metabolize DDT varied and only DDE was observed in cells of Skeletonema costatum, Cyclotella nana, Thalassiosira fluviatilis and Dunaliella tertiolecta (Bowes, 1972).

After application to spinach and cabbage, DDT slowly degraded. By means of thin-layer and gas chromatography and mass spectrometry, the following metabolites were identified: DDE, DDD, DDMU, DDA, DDA-conjugate and a DBH-conjugate (Zimmer and Klein, 1972).

Alfalfa was sprayed with a large concentration of DDT. Portions were then air dried in darkness, dried in sunlight and dried under ultra-violet lamps. Almost half (49%) of the DDT was lost during the drying process in the dark treatment, but no changes occurred to the DDT. On the fourth day of the ultraviolet treatment and the sixth day of the sunlight treatment, DDD was formed. No change occurred with the DDE in any of the treatments (Archer, 1969).

Wheat grains concentrate the bulk of the DDT in the germ. Experimental results indicated that some dehydrochlorination to DDE occurred while aerobic conditions persisted. When intergranular air was consumed, and

anaerobic conditions existed, degradation was by reductive dechlorination
to DDD. This apparently took place in parenchymal cells of the scutellum
and embryo of the germ. This was thought to be linked to anaerobic
peroxidation of unsaturated fats by iron porphyrin enzymes and might be
enhanced by carotenoid compounds (Rowlands, 1968). In ensiled pasture
herbage, DDT was extensively decomposed to DDD and DDE (Henzell and
Lancaster, 1969). Alfalfa, sprayed with DDT, was dried in the dark,
in sunlight and under UV lamps. No changes occurred to DDT in the dark
drying. In the other two processes, some DDE and DDD was formed
(Archer, 1969).

In a model ecosystem containing Sorghum halpense, Oedogonium cardiacum,
daphnia magna, Physa snails, gambusia affinis, and larvae of Culex
quinquefasciatus, in addition to unmetabolized DDT, both DDE and DDD
were observed. Some unidentified polar metabolites were also present
(Kapoor et al., 1970).

After susceptible and resistant larvae of the cattle tick Boophilus
microplus were exposed to labeled DDT, at least 17 metabolites were
isolated from both strains. Three metabolites were identified as
DDE, dicofol, and DBP. Six metabolites were characterized, but not
identified, as phenols and an aromatic carboxylic acid (Schnitzerling
et al., 1970).

When DDT-resistant houseflies were exposed to labeled DDT, DDE and
kelthane and unidentified conjugates were observed (Kapoor et al.,
1970).

In the codling moth (Carpocapsa pomonella), DDT was metabolized to
DDE; but the low rate of detoxification of absorbed DDT suggested
that dehydrochlorination was not the major mechanism of resistance
to DDT in the strains Amieus and Burnley used (Rose and Hooper, 1969).
DDTases, found in several insect species, have exhibited differences
in substrate affinity, catalytic activity, and susceptibility to
inhibitors. Differences in distribution of the DDT-dehydrochlorinases
within and between insects have also been demonstrated. Activity did
not always parallel distribution but metabolism generally proceeded
via DDE (Dinamarca et al., 1969; Quarishi et al., 1969; Khan, 1969).
Similarly in vitro dehydrochlorination of DDD by extracts of pupae
of the Mexican bean beetle (Epilachna Varivestis) gave rise to the
ethylene analog (Nettles and Swift, 1970).

A strain of the grain weevil Sitophilus granarius (L). resistant to
pyrethrins and DDT was exposed to DDT. Eight products were obtained
and six identified as: kelthane (major product), DDD, DDE, DDA, DBP,
and FW 152 [1,1-dichloro-2,2-bis(p-chlorophenyl)ethanol]. Another
was partially resolved as a complex glycoside which, upon treatment
with acid, yielded five products. Three were identified as

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3-hydroxy-4-chlorobenzoic acid, 4-hydroxybenzoic acid, and glucose. Using ring-labeled DDT, labeled conjugates of 4-hydroxybenzoic acid and ring-labeled 3-hydroxy-4-chlorobenzoic acid were obtained.

With a susceptible strain of weevil on wheat treated with DDT, DDE was the main product and only traces of DDD and DDA were produced (Rowlands and Lloyd, 1969).

DDT was not metabolized in adult and larvae of the khapra beetle (Trogoderma granarium Everts) (Gupta et al., 1971).

Studies were undertaken to understand the mechanism of DDT resistance in the mosquito Culex pipiens fatigans. Dehydrochlorination of DDT did not explain the resistance observed. The role of lipids was investigated. Although there was no evidence of correlation between lipid content and DDT resistance, among a single batch of larvae, the individuals that survived exposure to DDT exhibited a higher total lipid content than those that died (Kalra, 1970).

Laboratory studies supported field data that the chief metabolite of p,p'-DDT in worms (Allolobophora caliginosa, Sav.; Lumbricus terrestris L.) is p,p'—DDE while in slugs (Agriolimax reticulatus Muller) it is p,p'-DDD. In beetles (Carabidae), the breakdown of DDT to DDE occurs rapidly (Davis and French, 1969).

Rumen bacteria progressively converted DDT-^{14}C to DDD. Some DDE and a compound tentatively identified as DDMU were also observed. At the end of 48 hours, DDD accounted for 54% of the recovered activity. The data indicated reductive dechlorination rather than a two step reaction via DDE (Fries et al., 1969; Kutches and Church, 1971; Sink et al., 1972).

DDT and DDE were incubated with several species of microorganisms isolated from surface-ripened cheese. One isolate, thought to be a geotrichum isolate, did not form DDD. Geotrichum candidum and Brevibacterium linens degraded DDT and DDE. However, the products were not identified (Ledford and Chen, 1969).

Intestinal contents of 25 adult anchovies were drained into a sterile tube. Incubation with DDT gave rise to DDD and little or no DDE. While both bacteria and fungi metabolized DDT to DDD, it was found that fungi were primarily responsible for further degrading DDD to a water soluble product in anaerobic conditions (Malone, 1970).

E. coli converted DDT to DDD (75%) and DDE (25%) (Keil et al., 1972). In studies designed to ascertain the site of DDT metabolism in E. coli, neither the cytoplasmic fraction nor cytoplasmic fraction plus boiled membrane fraction exhibited appreciable ability to degrade DDT. However, in the presence of membranes not boiled plus the cytoplasmic fraction, DDT was converted to DDD in substantial amounts. These studies indicated that the stimulation of DDD production by FAD was dependent on anaerobic
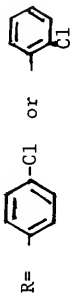
conditions; and, that the reductive dechlorination of DDD occurred in the membranous portion of the bacterial cell (French and Hoopingarner, 1970).

A Hydrogenomonas was isolated from sewage by enrichment techniques. This organism was incubated with DDT, p,p'-dichlorobenzophenone, p,p'-dichlorobenzhydrol, and p,p'-dichlorodiphenylmethane. Suspensions of washed cells neither grew nor cometabolized DDT or p,p'-dichloro-benzophenone. Dichlorobenzhydrol and dichlorodiphenylmethane were cometabolized. When the latter was incubated with a washed cell suspension, p-chlorophenylacetic acid was isolated. The latter was also cometabolized when incubated with Hydrogenomonas Yellow oils, which did not crystallize and did darken to reddish-brown colors after 24 hours, were obtained (Focht et al., 1970; Focht and Alexander, 1970a and 1970b, 1971).

Extracts of Hydrogenomonas sp. cells were incubated with ^{14}C-DDT. Under anaerobic conditions, in addition to unchanged DDT, the following compounds were produced: DDD, DDE, DDMU, DDMS, DBP, and very small amounts of DDNU, DDA, DDM and DBH. When these cultures were subsequently exposed to atmospheric oxygen, quantitative changes occurred with respect to the metabolites and a new compound p-chlorophenylacetic acid (PCPA) was produced. Aerobic incubation of PCPA with Arthrobacter sp. produced p-chlorophenylglycolaldehyde. When labeled DDT was added to sewage or freshwater sediment, the metabolite pattern was similar to that produced by Hydrogenomonas sp. in vitro. No PCPA was accumulated and the evidence indicated that it probably was not form (Pfaender and Alexander, 1972).

In studies with "mexed" cultures of Hydrogenomonas and a hyaline Moniliaceae fungus, the DDT metabolites DDM and -chlorophenylacetic acid were cometabolized to CO_2, H_2O and HCl (Focht, 1972).

Studies with extracts of bacteria, yeast and actinomycetes indicated that the cytochrome system was directly responsible for reductive dechlorination of DDT (Johnson, 1969).

DDD accumulated in DDT-treated flooded rice soil (Castro and Yoshida, 1971). In an anaerobic soil, in addition to DDD, DDT conversion produced traces of six other products: DDE, DBP, DDD, kelthane, DDA and BA. After sic months of aerobic incubation, 75% of the added DDT was recovered from the soils. Small amounts of DDE and a trace of DDE were observed (Guenzi and Beard, 1968).

Microorganisms, isolated from water and bottom silt of Lake Michigan and related water systems, were incubated with labeled DDT. The principal metabolite found was DDD (TDE). A number of isolates forming

Disappearance of DDE

pH	Recovery of DDE, %	
	7 days	28 days
10.0	91.7	87.8
13.0	93.9	73.6

Effect of pH on DDD→DDMU

pH	Recovery, %			
	7 days		28 days	
	DDD	DDMU	DDD	DDMU
10.0	94.1	----	91.3	----
13.0	6.0	82.9	5.5	45.2

(Smith and Parr, 1972)

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DDD also produced DDNS [1,1-bis(p-chlorophenyl)ethane] (Matsumura et al., 1971).

DDT, incubated with activated sludge, was rapidly consumed with a half-life of 7 hours. DDT was transformed to DDD, DBP, DDMU and a new compound identified as bis(p-chlorophenyl)acetonitrile [DDCN]. In ethanolic KOH, DDCN underwent autooxidation to DBP. DDCN has also been found in natural systems--the sediment layer of Lake Malaren in Sweden and from sewage sludge of a water treatment plant at Uppsala. Some DDE was also seen but disappeared within 48 hours (Albone et al., 1972; Jensen et al., 1972).

After exposure of <u>Fusarium oxysporum</u> to DDT, DDD and DDE were observed (Franzke et al., 1970). DDT was also degraded to DDD and DDE by molds growing on carrot puree (Engst et al., 1967).

^{14}C-DDT was added to four soils ranging from loamy sand to clay. Volatilization was determined at 30°C and 55°C. The soils were initially wetted. After the soils contained less than a monolayer of water, DDT was not volatilized at either temperature. Volatilization rates seemed to be inversely related to the soil surface area. Conversion of DDT to DDE ranged from 6.7% for the loamy sand soil to 21.2% for the silty clay loam (Guenzi and Beard, 1970).

In other studies with homoionic clays, DDT underwent some decomposition to DDE when placed on columns and allowed to diffuse. Homoionic acid bentonite, homoionic sodium bentonite, homoionic acidic vermiculite and homoionic sodium vermiculite were used. The decomposition of DDT into DDE was greater in the sodium samples than in the acidic ones; but this could be expected from perusal of the equation for the dehydrohalogenation process of DDT. In a basic medium, the equilibrium would be towards the formation of DDE (Lopez-Gonzalez).

Anerobic breakdown of DDT in soils is accelerated by glucose and by volatiles present in ground alfalfa. The order of effectiveness was acetaldehyde=isobutyraldehyde > ethanol > glucose >> methanol. The conversion of DDT to DDD in soil was shown to be microbial and highly sensitive to oxygen. Two percent oxygen inhibited DDT disappearance for 35 days (Burge, 1971).

The rate of degradation of DDT was related to the rate of formation of ferrous iron in soils containing organic matter and free iron and amended with urease. A mechanism was proposed whereby electrons furnished by the reduced organic substrate were transferred to DDT via ferrous ions, thereby initiating a free radical reaction in the absence of oxygen (Glass, 1972).

Photolysis of DDT did not occur unless an inducer with low ionization potential was present. At 3100 angstroms and in the presence of diethylaniline, photolysis of DDT yielded DDE, DDD, DBP and HCl. The

DDT-diethylaniline mixture was stable in the dark (Miller and Narang, 1970).

After UV irradiation of solid DDT, the reaction mixture was separated by TLC and GLC. Degradation products found included DDD, DDE and the benzophenone. UV irradiation of hexane solutions of DDT gave rise to DDD, DDE, HCl and some unidentified products (Mosier et al., 1969). The wavelength of irradiation determined the nature of the products. At 2600 A, there was loss of chlorine from the trichloromethyl group of DDT; at shorter wavelengths, chlorine is displaced from the aromatic ring. After irradiation of DDT in methanol solution, more than 30 compounds were found. When DDE was irradiated in methanol, in addition to products 2,3,7,8,11,14,16,18,21,28,29,30 (See Table), other compounds were found:

$RCH_2CO_2CH_3$ ClR_2CO

$ClRCO_2CH_3$ 3,6-Cl_2-9-dichloromethylene-
                                            fluorene

$R_2C=CH_2$
                                        $R_2C(OCH_3)CO_2CH_3$
3,6-Cl_2-fluorenone
                                        Unknown
3,6-Cl_2-9-Chloromethylenefluorene
                                        $ROCH_3$

R=   Cl-⟨ ⟩-   4-Cl-dimethylphtalate
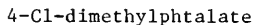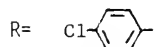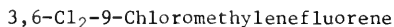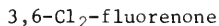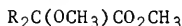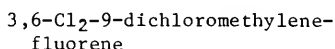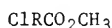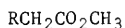
Some differences were found between irradiation in the presence of oxygen and in the absence of oxygen. A reaction sequence was postulated (Plimmer and Klingebiel, 1969a,b; Plimmer et al., 1970b).

$$R_2CHCCl_3 \xrightarrow{\text{light}} R_2CH\dot{C}Cl_2 + \dot{C}l \tag{1}$$

$$R_2CH\dot{C}Cl_2 + CH_3OH \longrightarrow R_2CHCHCl_2 + \dot{C}H_2OH \tag{2}$$

$$R_2CHCHCl_2 \xrightarrow{\text{light}} R_2CH\dot{C}HCl + \dot{C}l \tag{3}$$

$$R_2CH\dot{C}HCl + CH_3OH \longrightarrow R_2CHCH_2Cl + \dot{C}H_2OH \tag{4}$$

In the presence of oxygen

$$R_2CH\dot{C}Cl_2 + O_2 \longrightarrow R_2CHCCl_2 (\dot{O}_2) \tag{5}$$

$$2R_2CH\dot{C}Cl_2 (\dot{O}_2) \longrightarrow 2R_2CHCCl_2\dot{O} + \dot{O}_2 \tag{6}$$

$R_2CHCCl_2\overset{\cdot}{O}$ -----> $R_2CHCOCl$ + $\overset{\cdot}{C}l$ (7)

$R_2CHCOCl$ + CH_3OH -----> $R_2CHCOOCH_3$+HCl   (8)

R_2CHCCl_3+$\overset{\cdot}{C}l$ -----> $R_2\overset{\cdot}{C}CCl_3$+HCl   (9)

$R_2\overset{\cdot}{C}CCl_3$+$O_2$ -----> $R_2C\overset{\cdot}{O}_2CCl_3$ (10)

$2R_2C\overset{\cdot}{O}_2CCl_3$ -----> $2R_2\overset{\cdot}{C}OCCl_3$+ O_2 (11)

$R_2\overset{\cdot}{C}OCCl_3$ -----> R_2CO + $\overset{\cdot}{C}Cl_3$ (12)
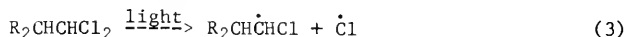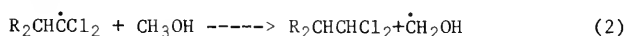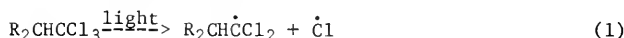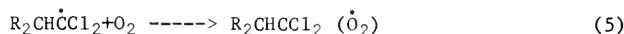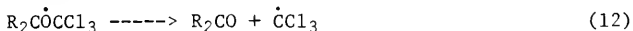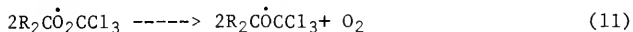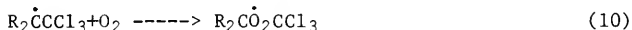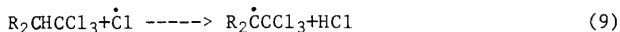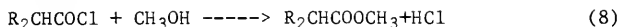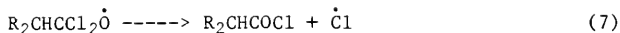
In the presence of isopropanol, DDD, acetone and HCl were formed from DDT when the solution was irradiated with ultraviolet light (Sherman et al., 1971).

UV irradiation of DDE in hexane produced p,p'-dichlorobenzophenone, 1,1-bis(p-chlorophenyl)-2-chloroethene, a photoisomerization product, and two compounds resulting from the reaction of DDE with the solvent. In the gas phase, the only compounds observed were TDEE and the photoisomerization product (Kerner et al., 1972).

A mixture of DDT-tristearin- water was subjected to γ-radiation. Products formed were identified as hydrogen, DDE, DDT dimer, DDT-tristearin addition product-hexane soluble and hexane insoluble (Kimbrough and Gaines, 1971).

When DDT was heated in metal containers, there was a progressive loss of DDT and accumulation of DDD. In the presence of metallic tin and ammonium chloride, when DDT was heated at 110-115°C for eight hours, practically all DDT was degraded to DDD, DDE, DDA and three unknown components. Some degradation to these products also occurred when DDT was heated in aqueous dioxane alone (De Loach and Hemphill, 1971; Singh and Malaiyandi, 1969).

An interaction between DDT and lecithin was indicated by the reciprocal effects of each compound on the proton magnetic resonance spectrum of the other. The phosphoryl choline moiety of the lecithin and the benzylic proton of the DDT seem to be involved (Tinsley et al., 1971).

Kelthane was applied to apples which were then processed to pomace. The pomace was divided into 3 equal amounts and dried. Whether dried in the dark, by UV or sunlight, kelthane and 4,4'-dichlorobenzophenone were present (Archer and Toscano, 1972).

After UV irradiation of almond hull meal, the major product detected was 4,4'-dichlorobenzophenone (Archer, 1970).

Chemical studies with kelthane, the 2-hydroxy analog of DDT, showed that under the same conditions kelthane was converted quantitatively to DBP while acetylkelthane yielded 74% DDE and a small amount of

DDMU. It was concluded that kelthane was as good, if not better, a precursor of DDE than was DDT. Thus, DDE formation could be considered a one-step dehydrochlorination or a two-step dehypochlorination (McKinney and Fishbein, 1972).

UV IRRADIATION OF DDE IN HEXANE

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Table 1

R$_1$ = Cl-⟨benzene⟩-

R$_2$ = ⟨benzene⟩-
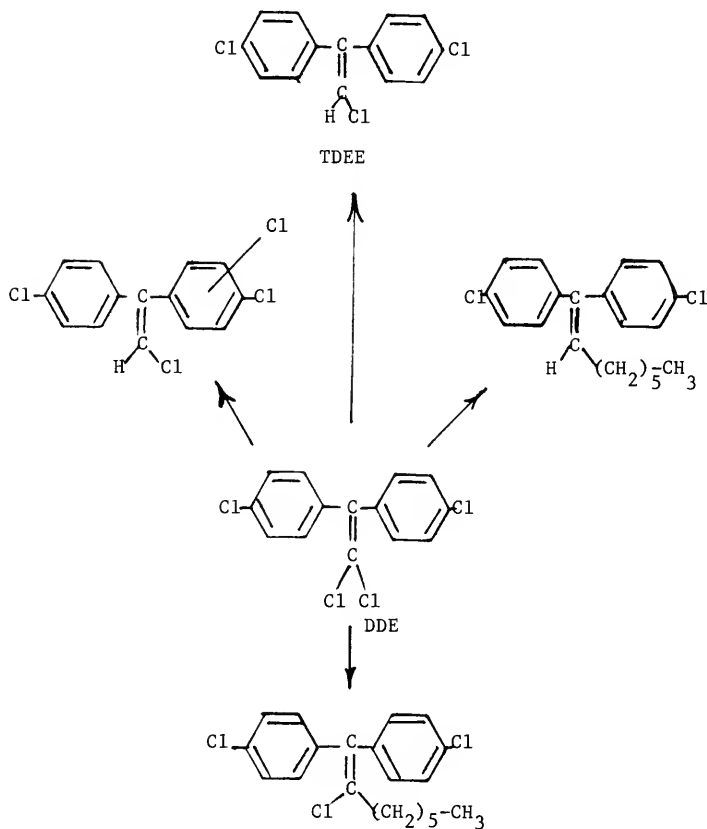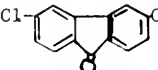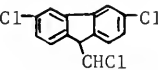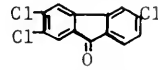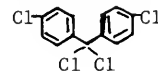
Photolysis Products of DDT and DDE

Compound	DDT		DDE	
	O$_2$	N$_2$	O$_2$	N$_2$
1. R$_2$—C(=O)-OCH$_3$	+	−	−	−
2. R$_1$—CHO	+	−	+	
3. R$_1$—COOCH$_3$	+	+	+	+
4. (R$_2$)$_2$-C = CH$_2$	+	+	−	−
5. R$_1$—CH$_2$-COOCH$_3$	−	−	+	+
6. Cl-⟨benzene-Cl⟩—COOCH$_3$	−	−	+	−
7. R$_2$ R$_1$—C = CH$_2$	−	+	+	+
8. (R$_1$)$_2$	+	+	+	+
9. (R$_2$)$_2$—CH-COOCH$_3$	−	+	−	−
10. R$_2$ R$_1$—CHOCH$_3$	+	+	−	−
11. (R$_1$)$_2$-CH$_2$	+	+	+	+
12. (R$_1$)$_2$—C = CH$_2$	−	−	−	+
13. Cl-⟨fluorene⟩-Cl (C=O)	−	−	+	−
14. (R$_1$)$_2$—C = O	+	+	+	+
15. R$_2$ R$_1$—CH—COOCH$_3$	+	+		
16. (R$_1$)$_2$—CHOCH$_3$	+	+	+	+
17. Cl-⟨fluorene⟩-Cl CHCl	−	−	+	
18. (R$_1$)$_2$—C = CHCl	+	+	+	+
19. R$_2$R$_1$—CH-CH-Cl$_2$	+	+	−	−
20. Cl-⟨fluorenone⟩-Cl (O)		−	+	
21. (R$_1$)$_2$CH-COOCH$_3$	+	+	+	+
22. Cl-⟨⟩-⟨⟩-Cl, Cl Cl	−	−	+	−
23. DDE	−	+		
24. DDD	+	+	−	−
25. (Cl-⟨benzene⟩-)$_2$C(OCH$_3$)-COOCH$_3$	−	−	+	
26. R$_1$OCH$_3$				
27. Cl$_2$—R$_2$CO$_2$CH$_3$				
28. Cl$_2$—R$_2$O CH$_3$				
29. Cl$_3$—R$_2$OCH$_3$				
30. 3,3'-Cl$_2$-6-CO$_2$CH$_3$-biphenyl				

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DDVP (Dichlorvos, Nogos, Nuvan, Vapona, Dedevap) [2,2-Dichlorovinyl dimethyl phosphate]

(See also Trichlorphon)

Vinyl-1-[14]C- and [36]Cl-dichlorvos was administered orally to male and female rats. Excretion patterns were the same in both sexes. The major metabolite from the vinyl carbons was CO_2. Urine analyses indicated the presence of nine compounds. Those identified were hippuric acid (8.3%), 2,2-dichlorovinyl methyl phosphate (10.9%), 2,2-dichloroethyl- -D-glucopyranosiduronic acid (27%) and urea (3.1%). Considerable radioactivity was also retained in the liver as glycine, serine, cystine and aspartate (Hutson et al., 1971).

The bimolecular rate constant for the inhibition of bovine erythrocyte cholinesterase was determined at 37°C to be $1.56 \times 10^4 \, M^{-1} min^{-1}$ (Braid and Nix, 1969).

In rats, DDVP was degraded by two enzymatic pathways. One path, glutathione dependent, procedes via demethylation to desmethyl DDVP. In the second route, not dependent upon glutathione, DDVP was metabolized via hydrolysis to dimethyl phosphate and dichloroacetaldehyde. Desmethyl DDVP metabolism to monomethyl phosphate and dichloro-acetaldehyde was glutathione - independent also (Dicowsky and Morello, 1971).

Four days after oral administration of vinyl-1-[14]C- DDVP to male rats, about 44% of the label was found in the carcass; 39% appeared as CO_2; and 13% was excreted in urine; and 3.4% was found in the feces. Nine labeled metabolites were found in the urine and included dichloro-ethyl β-D-glucopyranosiduronic acid, dichlorovinyl methyl phosphate, N-benzoyl glycine, and urea. In the liver, radioactivity was identified as glycine-^{14}C and serine-[14]C. Administration of DDVP as a vapor gave similar results (Hutson et al., 1971).

After administration of DDVP to young pigs, analyses showed the presence of demethyl DDVP, dichloroacetaldehyde, dichloroethanol, and dichloroacetic acid in the intestinal lumen but only the dichloroethanol in portal or peripheral blood. Fractionation of liver and muscle tissue showed that the vinyl carbon entered glycine, serine and, at lower levels, glucose, cholesterol, fatty acids, and RNA. With blood and lung tissue, DDVP was rapidly degraded to demethyl DDVP and methyl phosphate esters (Page et al., 1971; Loeffler et al., 1971).

When applied to stored wheat, DDVP underwent rapid degradation to dimethyl phosphate and phosphorylated protein derivatives (Rowlands, 1970).

Half-life at $37.5^{o}C$	
System	DDVP
Buffer, pH 7.0	28 hr
Buffer, pH 8.0	16
Cow blood, pH 7.7 (in vitro)	1.2

(Kuhnert et al., 1963).

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DFP [Diisopropyl fluorophosphate]

Hen egg-white lysozyme was allowed to react with an excess of DFP at 25°C and at pH values ranging from 9.5 to 11.0. Analyses indicated that alkylphosphorylation of the tyrosyl hydroxyl groups had occurred and that some other amino acid residues had also been phosphorylated (Murachi et al., 1970). Similar results were obtained with stem bromelain, Taka-amylase A, and papain. In the case of ficin, seryl (and/or threonyl) residues were phosphorylated (Chaiken and Smith, 1969; Gould and Liener, 1965; Murachi, 1963; Murachi and Yasui, 1965; Murachi et al., 1965).

DIALLATE   [S-2,3-dichloroallyl-N,N-diisopropylthiolcarbamate]

EPTC   [S-ethyl-N,N-dipropylthiolcarbamate]

PEBULATE   [S-propyl-N,N-butylethylthiolcarbamate]

TRIALLATE   [S-2,3,3-trichloroallyl-N,N-diisopropylthiolcarbamate]

VERNOLATE   [S-propyl-N,N-dipropylthiolcarbamate]

When diallate, EPTC, pebulate, triallate or vernolate was applied
to soil, 50% was lost within 2 to 4 weeks. EPTC, pebulate and
vernolate were not affected by treatment with 10N sodium hydroxide
at 95°C for 1 hour; but diallate and triallate were degraded in
alkali under much milder conditions (Smith and Fitzpatrick, 1970).

Labeled EPTC was administered orally to adult female rats in doses
of 0.6 to 103 mg. With increased doses, $^{14}CO_2$ decreased but
urinary excretion of radioactivity increased. Chromatography
revealed six major metabolites in the urine. One was identified
as urea. Three others not identified exhibited a labile nature
(Ong and Fang, 1970).

At rates of application equivalent to 0.75 to 3 lbs. per acre,
50% of the triallate applied was degraded in 8 to 11 weeks at 25°C
in moist Regina heavy clay and Weyburn loam. In sterile soils,
there was no loss (Smith, 1969). In other field plots, 16 to 27%
of the applied triallate was found in the top 5 cm of soil after
one growing season (5 months) (Smith, 1971).

In cultural studies, two penicillium molds absorbed triallate onto
the mycellium in such a manner that the material was poorly extracted
by benzene but extractable by a benzene-isopropanol mixture (Cullimore
and Smith, 1972).

When treated with methanolic KOH, triallate yielded a compound
identified as cis-S-2,3,3-trichloroprop-1-ene N,N-diisopropylthiol-
carbamate (Smith and Rummens, 1971).

DIAZINON   [O,O-Diethyl-O-(2-isopropyl-4-methyl-6-pyrimidinyl)
            phosphorothioate]

After oral administration to rats, the excretion of ring and side
chain labeled diazinon exceeded 90% after 168 hours. The biological
half-life varied from 7 hours in male rats for ethyl-^{14}C diazinon
to 12 hours for 2-^{14}C-diazinon in male and female rats. No ring
cleavage took place. Four metabolites were observed in urine
and in feces. Spectroscopy and chromatography were applied to
identify the metabolites. The main degradative mechanism was
hydrolysis and oxidation of the isopropyl side chain at the
primary and tertiary carbons. Three metabolites were identified:
5,6-dihydro-2-isopropyl-4-methyl-6-pyrimidinone (IIIa) and the
corresponding 1-hydroxy- (VII) and 2-hydroxyisopropyl (IV) analogs
(Mucke et al., 1970).

Diazinon and diazoxon metabolism was studied with subcellular
fractions of rat liver homogenates. The results suggested that
a hydrolase system, independent of NADPH, hydrolyzed diazoxon
and not diazinon. In the presence of microsomes and NADPH,
oxidation of diazinon yielded diazoxon (II). Diethyl phosphoric acid
and diethyl phosphorothioic acid were also observed (Yang et al.,
1969 and 1971a).

After administration of diazinon by stomach tube to a sheep,
hydroxydiazinon was found in the tissues. Diazinon, when fed
to sheep, was metabolized also by hydroxylation of the C-4 methyl
group. Residues of this and the C-1' isopropanol analog were
found in all tissues examined and in urine. The proportion of
the C-4 analog was higher in urine than in the tissues (Machin
et al., 1972). Hydroxy-diazinon was also observed after incubation
of guinea-pig liver slices with diazinon (Machin et al., 1971).

After treatment of crops with diazinon, the oxygen analog was
present at low levels by the end of 7 days (Eberle and Novak, 1969).
On field sprayed kale, in addition to diazoxon, hydroxy-diazinon and
2-isopropyl-4-methyl pyrimidin-6-ol were also detected.   The
hydroxy-diazinon probably arose from natural UV irradiation of
diazinon (Pardue et al., 1970).

Microsomal preparations have been made from resistant and non-
resistant strains of houseflies. The rate of diazinon oxidation
was found to be greater in resistant than in non-resistant strains.
Other microsomal activities, such as N- and O-demethylation are
higher in diazinon resistant houseflies. In addition to diazoxon,
diethyl phosphoric and phosphorothioic acids were formed (Elbashir
and Oppenoorth, 1969; Folson et al., 1970; Yang et al., 1971b).

In mice, diazinon was converted to diazoxon, the α-hydroxypropyl derivative, the 2-propenyl derivative, the α-hydroxyethyl derivative, the hydroxymethyl and formyl derivatives (Sekine, 1972).

Microsomal preparations from rat liver and American cockroach fat body were used to study the metabolism of diazinon. Both systems fortified with NADPH or NADH altered diazinon via sulfur removal, alkyl side chain hydroxylation and cleavage of the ring-P bond. The major metabolites were biologically active and included: hydroxydiazinon, diazoxon and hydroxydiazoxon. Other metabolites were identified as 2-hydroxy-4-methyl-6-isopropylpyrimidine; 2-hydroxy-6-(2'-hydroxyisopropyl)-4-methylpyrimidine; diethyl phosphorothioate; and diethyl phosphate. The rat liver enzyme system showed a higher rate of oxidative metabolism than the American cockroach fat body system. EDTA stimulated the overall diazinon metabolism (Shishido et al., 1972a).

Hydrolytic activities of rat tissues for diazoxon was liver > blood > lung > heart > kidney > brain. A microsomal enzyme hydrolyzed diazoxon to diethyl phosphate and the corresponding hydroxypyrimidine. The enzyme was inhibited by EDTA, rare earth and heavy metal ions, and SH reagents; but Ca^{2+} activated the enzyme and protected it from inactivation. Hepatic and serum mitochondrial and soluble enzymes hydrolyzed diazoxon and were also activated by Ca^{2+}. Removal of protein-bound calcium by dialysis against EDTA gave a partially irreversible change of the enzyme. Diazoxon hydrolysis did not occur with American cockroach homogenates (Shishido and Fukami, 1972).

Cleavage of the pyrimidinyl-P bond of diazinon or diazoxon by soluble enzyme preparations produced diethyl phosphorothioate and S-(2-isopropyl-4-methyl-6-pyrimidinyl) glutathione. Although this activity was present in several tissues in cockroach and rat, highest activity was found in the fat body and liver, respectively. The transferase was specific for glutathione but was also active for other alkyl homologs of diazinon. The pH optima were 6.5 for the fat body and 6.0 for the liver enzyme. Both enzymes were inhibited by SH reagents, oxidized glutathione, and some chelaters. Fat body enzyme was markedly sensitive to o-phenanthroline (Shishido et al., 1972b).

In vitro metabolism of diazinon by hepatic subcellular fractions of channel catfish (Ictalurus punctatus) produced diazoxon and some polar metabolites: diethyl phosphorothioic acid and diethyl phosphoric acid. Similar results were obtained with hepatic microsomes from bluegill, Lepomis macrochirus (Hogan and Knowles, 1972).

When houseflies were exposed to diazinon, the 4-carboxyl analog was detected (Sekine, 1972) in addition to diethyl phosphorothioate and diethyl phosphate (Lewis and Lord, 1969).

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In studies with subcellular fractions prepared by differential centrifugation of whole-fly homogenates, three detoxification mechanisms were found. In the microsomal fraction, cleavage of diazinon and diazoxon to diethyl phosphorothioic acid and diethyl phosphoric acid, respectively, occurred and required oxygen. NADPH and GSH separately increased metabolism five-fold and ten-fold when together. The synergist Sesamex inhibited the mechanism; but $\underline{S},\underline{S},\underline{S}$-tributylphosphorotrithioate (TBTP), a synergist and aliesterase inhibitor, did not inhibit this mechanism. This pathway was present in all strains tested, resistant and non-resistant.

The second mechanism, involving desethylation of diazinon and diazoxon, occurred in the soluble fraction of strains with gene a and required GSH as cofactor. Monoethyl esters of phosphorothioic and phosphoric acids were detected. NADPH and oxygen were not required for desethylation, which was greater in their absence. Sesamex had no effect on this mechanism but TBTP inhibited it.

The third mechanism occurred in the microsomal fraction of strains with the gene for resistance on chromosome V. Diazinon was not degraded. Diazoxon was degraded to two metabolites not identified. NADPH and oxygen were required. Sesamex inhibited this mechanism; TBTP did not (Lewis, 1969).

In other studies, carboxylesterase activity was inversely correlated to diazoxon degradation capacity and resistance values among resistant housefly strains. The total resistance of most highly resistant flies was not completely explained on the basis of toxicant breakdown. This indicated the presence of other resistance factors in those strains most highly resistant (Collins and Forgash, 1970; Lewis and Sawicki, 1971).

After topical treatment of Western corn rootworm beetles (<u>Diabrotica</u> <u>virgifera</u> Leconte) with labeled diazinon, the diazinon was rapidly absorbed and degraded. Chromatographic analyses detected the presence of diazoxon, the hydroxy pyrimidine, and mercaptopyrimidine. Small amounts of CO_2 arose from side chain oxidation (Conaway and Knowles, 1969).

After repeated applications of diazinon granules to soil surface of rice fields, a factor was present that caused rapid degradation of diazinon. This factor was present in the paddy water, in the rhizophere soil of the rice plant, and in non-rhizosphere soils. When incubated with water from diazinon treated fields, diazinon was rapidly hydrolyzed (about 75 hours) to 2-isopropyl-6-methyl-4-hydroxy-pyrimidine. Complete degradation to CO_2 occurred within another 25 hours. Addition of streptomycin prevented the diazinon breakdown (Sethunathan and Pathak, 1972). Diazinon was absorbed rapidly by

rice roots when applied to paddy water and translocated to leaf
sheath and leaf blades. Residues were at maximum 5 days after
application but then declined rapidly. This loss was greater
after the second application. Inactivation of diazinon by water
from treated fields was retarded if incubation mixtures were
sterilized or kept anaerobically. Release of $^{14}CO_2$ from labeled
diazinon was rapid from water of treated fields. Streptomycin
inhibited the system. A bacterium (<u>Arthrobacter</u> sp.) capable of
metabolizing diazinon in the presence of ethanol and glucose was
isolated from water of treated fields. A <u>Streptomyces</u> sp. has also
been reported capable of degrading diazinon in the presence of glucose.
Under submerged conditions, diazinon was degraded to 2-isopropyl-4-
methyl-6-hydroxy pyrimidine. No diazoxon was detected. Further
degradation of the hydroxypyrimidine does not occur under the
anaerobic conditions of the submerged soil (Sethunathan, 1971a and 1971b;
Sethunathan and MacRae, 1969; Sethunathan and Yoshida, 1969;
Sethunathan and Pathak, 1971; Sethunathan et al., 1971).

Using labeled diazinon, radiochromatograms of rice sheath showed the
presence of diazinon, diazoxon, the α-hydroxypropyl derivative and
an unidentified compound after application of diazinon to rice in the
field (Sekine, 1972).

About 50% of the diazinon was lost from treated rice plants within
9 days through volatilization from the paddy water and transpiration
from the leaves. Less than 10% of the radioactivity remained in the
plants as the parent compound. Metabolites found in the plant were
identified as: 2-isopropyl-4-methyl-6-hydroxypyrimidine; 2-(1'-
hydroxy-1'-methyl)ethyl-4-methyl-6-hydroxypyrimidine, free and as a
glucoside; and a small fraction of polar metabolites. The same
metabolites and traces of diazoxon were found after stem injection of
diazinon. Another compound observed was thought to be hydroxy diazinon.
In pea plants, the hydroxy pyrimidine and its isopropanol analog were
observed (Laanio et al., 1972).

1=Animal   2=Plant   3=Insect   4=Microorganism

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2,3-Dibromobutane

After inoculation of soil-water suspensions with dibromobutanes, bromine was eliminated. Butene was produced (Castro and Belser, 1968).

ETHYLENE DIBROMIDE (EDB) [1,2-Dibromoethane]

Incubation of ethylene dibromide at pH 7.0 with soil and water gave rise to ethylene and bromide ions. In about two months, EDB is converted almost completely and quantitatively (Castro and Belser, 1968).

1,2-Dibromo-3-chloropropane (DBCP)

DBCP was converted by soil-water cultures to n-propanol, bromide and chloride. Maximum conversion was 63% in the course of 4 weeks. Allyl alcohol, a postulated intermediate, was seen in some experiments. Soil-water cultures converted allyl alcohol to n-propanol (Castro and Belser, 1968).

<u>DICAMBA</u> (Banvel, Mediben) [3,6-Dichloro-2-methoxybenzoic Acid]

In Tartary buckwheat (<u>Fagopyrum</u> <u>tataricum</u> L.), both in intact plants
and in detached leaves, dicamba was detected in conjugated form
only. The aglycone was identified as 5-hydroxy-3,6-dichloro-<u>o</u>-anisic
acid. Some decarboxylation of dicamba also occurred (Chang and
Vanden Born, 1971a). The 5-hydroxy metabolite was also observed in
wild mustard (<u>Sinapis</u> <u>avensis</u> L.), barley (<u>Hordeum</u> <u>vulgare</u> L.)
and wheat (<u>Triticum</u> <u>vulgare</u> L.). Additionally, a minor metabolite
identified as 3,6-dichlorosalicylic acid was found in barley and
wheat only (Chang and Vanden Born, 1971b).

<u>DICHLONE</u> (Phygon) [2,3-Dichloro-1,4-naphthoquinone]

After irradiation of a benzene solution of dichlone, an aliquot
was injected into a gas chromatograph and effluents corresponding
to peaks were collected separately. Compound 1 was identified by
IR as phthalic anhydride. The major photoproduct was identified
after IR and mass spectrometry as 2-chloro-3-phenyl-1,4-
naphthoquinone (White et al., 1969).
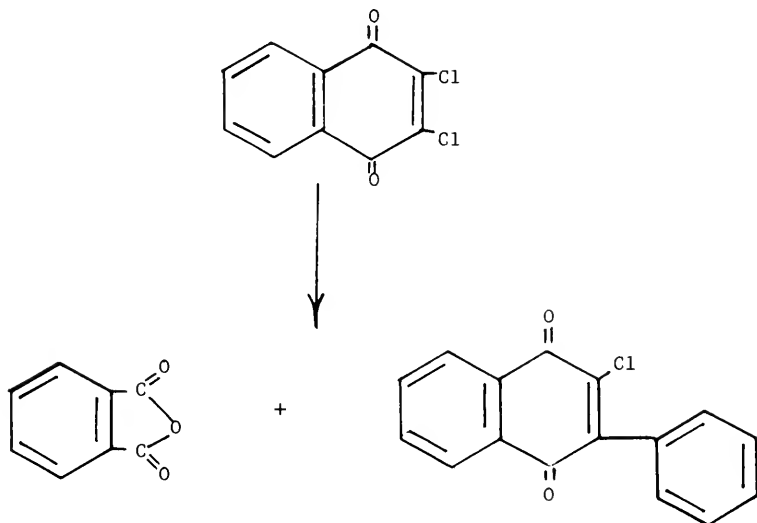
<u>DICRYL</u> (3',4'-Dichloro-2-methacrylanilide)

(See also Anilines)

An aryl acylamidase from tulip bulbs hydrolyzed dicryl. Tests
with the enzyme indicated a lack of sensitive sulfhydryl groups
and a pH optimum between 6.8 and 7.8. The apparent K_m was
2.50 x10^{-3}M with propanil as substrate (Hoagland and Graf, 1971
and 1972).

<u>0,0-Diethyl-0-(4-ethylphenyl) phosphorothioate</u>

After intraperitoneal administration of 0,0-diethyl 0-4-ethylphenyl
phosphorothioate in female mice, feces were collected and analyzed.
Neutral metabolites were not detected. In addition to p-ethyl-
phenol, p-(α-hydroxyethyl)phenol and p-acetylphenol were detected
(Eto et al., 1972).

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DIMEFOX (DMF) [Bis(dimethylamido)phosphoryl fluoride]

Hydrolysis (20°C)

pH	$t_{1/2}$	k (min^{-1})
2	2 hrs.	5.75×10^{-3}
3	16.5 hrs.	7.00×10^{-4}
4	8.2 days	5.88×10^{-5}
5	85 days	5.65×10^{-6}
11	93.5 days	5.15×10^{-6}
12	13 days	3.70×10^{-5}

(Koch et al., 1969)

<u>DIMETHIRIMOL</u> [5-n-Butyl-2-dimethylamino-4-hydroxy-6-methylpyrimidine]
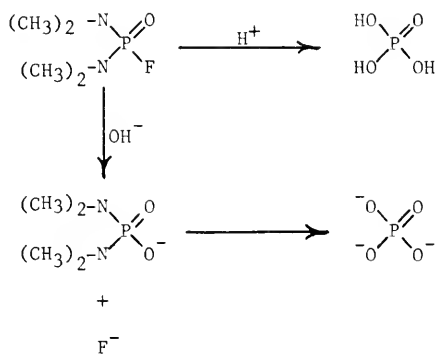
About 80% of labeled dimethirimol fed to rats was excreted within 48 hours in the urine. Five metabolites were isolated from urine and characterized and one was obtained from the bile. These are shown in the diagram (Calderbank, 1971).

In other studies, following administration of dimethirimol to dogs and rats, seven metabolites were identified in urine and bile (Bratt et al., 1972).

In cucumber plants grown in culture solution, dimethirimol half-life was about 24 hours. The <u>N</u>-demethyl analog formed rapidly. The second methyl group was lost more slowly. A mixture of water-soluble compounds were also formed and could be hydrolyzed to the dealkylated analogs (Calderbank, 1971).

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DIMETHOATE (Rogor) [O,O-Dimethyl S-(N-methylacetamide) phosphorodithioate]
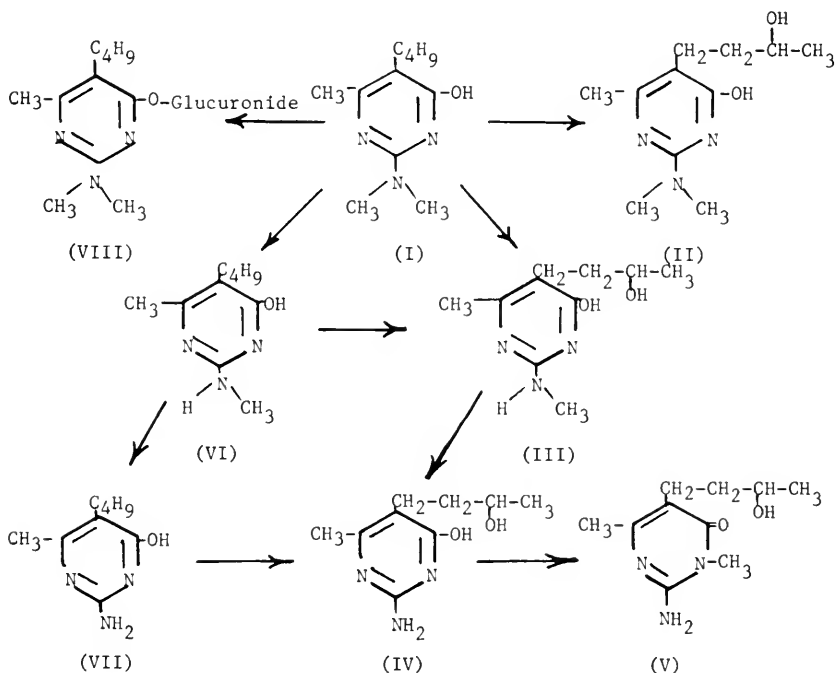
Twenty-four hours after administration of labeled dimethoate to rats, 60% of the dose was eliminated via urine and expired air. The major hydrolytic path proceded via C-N cleavage of dimethoate and probably of the oxon analog. Liberated methylamine was oxidized to CO_2 and traces of formate. Oxidation of dimethoate to dimethoxon also probably occurred in vivo. Esterase action acted on the S-C bond. After ^{32}P-dimethoate was administered to rats, the following compounds were found in urine:

1. Dimethoate
2. Dimethoxon
3. Dimethoate carboxylic acid
4. Dimethylphosphorodithioate
5. Dimethylphosphorothioate
6. Dimethylphosphate
7. Monomethylphosphate
8. Phosphorothioate
9. Formate
10. N-Methyl 2-glucuronate acetamide

Liver degraded dimethoate primarily to the carboxylate analog and dimethylphosphorodithioate (Hassan et al., 1969).

Three male and three female Sprague-Dawley white rats were administered labeled dimethoate via stomach tube. Urine was collected and analyzed. Five radioactive peaks were observed: the oxygen analog; N-hydroxymethyl dimethoate; des-N-methyl dimethoate; N-hydroxymethyl oxygen analog; and des-N-methyl oxygen analog. After 24 hours, recovery of radioactivity from male rats was about 7% greater than from female rats (Lucier and Menzer, 1970).

Rabbit and rat liver microsomes converted dimethoate to the oxygen analog and des-N-methyl derivatives. No N-hydroxymethyl compounds were detected (Lucier and Menzer, 1970).

Cultures of pure human embryonic cells oxidatively metabolized dimethoate. Chromatography indicated the presence of des-N-methyl analogs of dimethoate and dimethoxon, dimethoate carboxylic acid, des-O-methyl dimethoate carboxylic acid, and des-O-methyl dimethoate. NADPH was a required cofactor. When mouse fibroblast cells were used, only dimethoate carboxylic acid was observed (North and Menzer, 1972).

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Bean plants (Phaseolus vulgaris L.) were treated by foliar application. Six radioactive peaks were isolated. In addition to the five observed in rat urine, one other unidentified compound was found (Lucier and Menzer, 1970).

In adult larva of cotton leaf worm, labeled dimethoate was degreaded. Dimethoxon was the most abundant metabolite. Methylamine, released by carboxyamidase action, was oxidized to carbon dioxide. Phosphatase action released thiophosphate and then methanol. The latter was also oxidized to CO_2. Esterase activity split dimethoate into O,O-dimethyl phosphorodithioic acid and N-methyl hydroxyacetamide. The latter was excreted as a glucuronide (Zayed et al., 1970).

The penetration of analogs of dimethoate through the isolated gut of the hornworm (Manduca sexta L.), roach (Blaberus cranifer Burm.), and mouse (Mus musculus L.) was studied. Although toxicity varied by many fold, penetration rates varied by not more than two, an indication that penetration rates contributed little to selective toxicity. Compounds tested were the methoxy, ethoxy, n- and iso-propoxy and butoxy analogs of dimethoate (Shah et al., 1972).

DINITRAMINE (Cobex) [N,N-Diethyl-2,4-dinitro-6-trifluoromethyl-m-
                phenylenediamine]

In culture solutions of Aspergillus fumigatus Fres., Fusarium
oxysporum Schlect. and Paecilomyces sp., dinitramine(I) metabolism
produced a number of metabolites. Co-chromatography and mass
spectrometry were used to identify two products as: monodealkylated
dinitramine(II) and di-dealkylated dinitramine(III). More polar
metabolites were also present (Laanio et al., 1972).

When dinitramine was incorporated at 1/2 lb. per acre in Anaheim
silty loam soil, there was 20% loss from the soil. After 100 days,
the major component(II) was isolated, characterized and independently
synthesized. Compounds III and IV were characterized by TLC
(Smith, 1972).

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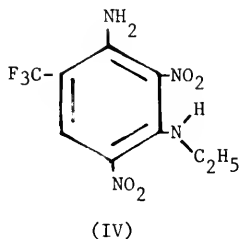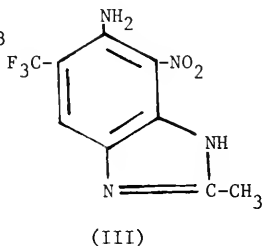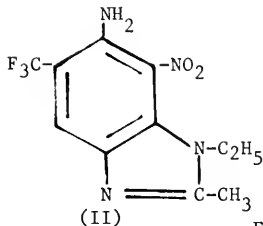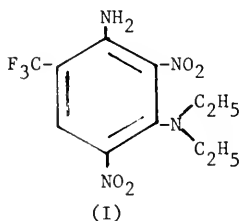
<u>DINOBUTON</u> [2-sec-butyl-4,6-dinitrophenyl isopropyl carbonate]

Rats and mice were fed labeled dinobuton. The organo-soluble
portion of rat urine contained 13 materials. Metabolites were
identified by co-chromatography as: DNBP free and conjugated,
DNBP-3-COOH free and conjugated, DNBP-2-COOH, $6-NH_2-NBP$ free
and conjugated, and 2-<u>sec</u>-butyl-4-acetamido-6-nitrophenol.
Using microsomes from rat liver and housefly abdomens, from
dinobuton DNBP, $6-NH_2-NBP$, and 13 unknowns were observed.

After injection of dinobuton into stems of bean plants, DNBP,
$4-NH_2-NBP$, and $6-NH_2-NBP$ were observed in conjugated form as
β-glucosides. Some CO_2 released by hydrolysis of dinobuton
was also incorporated into plant materials. On treated leaves,
were found compounds thought to be one of the isomeric
2-(hydroxy-<u>sec</u>-butyl)-and 2-(2-β-butenyl)-4,6-dinitrophenols.

Photoalteration of dinobuton gave 10-13 compounds. Several
compounds were tentatively identified as $6-NH_2-NBP$, DNBP, and
DNBP-3-COOH (Bandal and Casida, 1972).

In fresh sheep rumen fluid, Dinobuton was rapidly decomposed.
Simultaneously, the amount of 6-ANBP increased. The diamino-
phenol (DABP) was the end product of the ruminal metabolism
(Froslie, 1971).

DIOXIN   [Dibenzo-p-dioxin]*
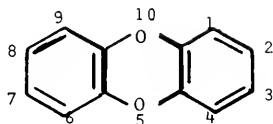
In methanol, chlorine substituents on the aromatic ring are replaced
by hydrogen when the dibenzo-p-dioxins are irradiated by light of
$\lambda \approx$ 300 nm or sunlight. Ultimately the heterocyclic ring was ruptured
(Plimmer et al., 1971).

Dioxins were irradiated as homogeneous solutions in methanol or ethanol.
Rate of hydrolysis was affected by the degree of chlorination. 2,3,7,
8-Tetrachlorodibenzo-p-dioxin gave rise to 2,3,7-trichlorodibenzo-p-
dioxin and a dichloro homolog. The octachloro analog gave rise to a
series of chlorinated dioxins. When the 2,3,7,8-tetrachloro compound
was added to soil or water and irradiated, decomposition was negligible
(Crosby et al., 1971).

2,7-Dichlorodibenzo-p-dioxin was slowly degraded in soil with evolution
of some CO_2 (Kearney et al., 1972).

2,3,7,8-Tetrachlorodibenzo-p-dioxin was somewhat stable at temperatures
up to 700°C. Decomposition was complete at 800°C (Stehl et al., 1971).

*Dioxins are not pesticides but are of concern because of their
 potential hazard and their presence as contaminants in phenoxy
 herbicides, particularly 2,4,5-T.

DIPHENAMID [N,N-Dimethyl-2,2-diphenylacetamide]

In winged euonymus (Euonymus alatus) and tomato (Lycopersicon esculentum), diphenamid was metabolized into two compounds. One was identified as the mono-N-demethylated diphenamid (Bingham and Shaver, 1971).

The metabolism of diphenamid in tomato and wheat was studied. Metabolites found in both plants included N-methyl-2,2-diphenylacetamide, 2,2-diphenylacetamide, and one unidentified compound. Whole tomato plants also contained a diphenamide glucoside (Schultz and Tweedy, 1971).

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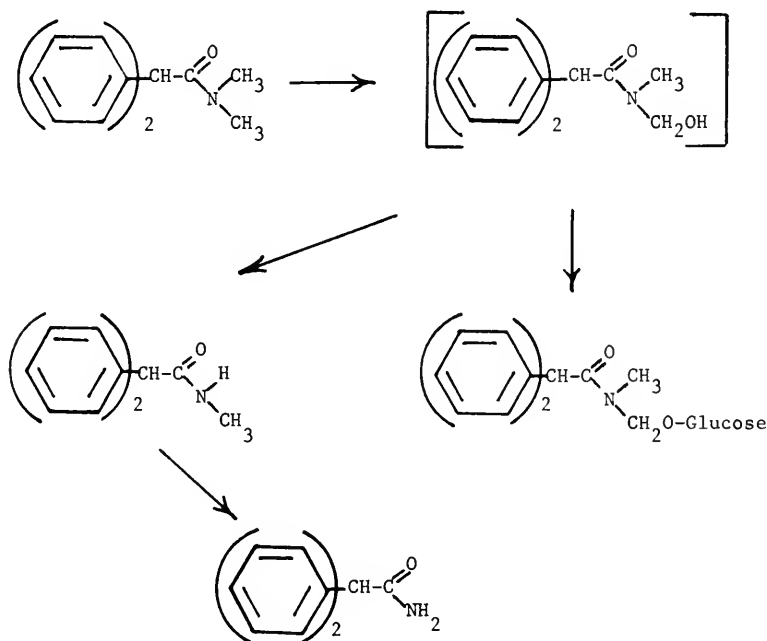
DIQUAT (1,1'-Ethylene-2,2'-dipyridinium dibromide) [6,7-Dihydro-
    dipyrido[1,2-a:2',1'-c]pyrazine]

Paraquat [1,1'-Dimethyl-4,4'-bipyridilium di(methyl sulfate) or
    dichloride]

A gram negative rod capable of utilizing picolinamide, a photo-
degradation product of diquat, as a sole carbon and nitrogen
source was isolated from soil. Suspensions of washed cells
grown on picolinamide were capable of oxidizing without lag
picolinate, 6-hydroxypicolinate, maleamate, and maleate. Both
picolinate and 2,5-dihydroxypyridine have been observed in the
supernatant of cultures oxidizing picolinamide. Picolinamide
and picolinate were oxidized stoichiometrically to 6-hydroxy-
picolinate. The latter accumulated in cultures inhibited with 5 mM-
sodium arsenite; pyruvate accumulated in cultures inhibited with
1 mM sodium arsenite. 2,5-dihydroxypyridine was converted into
maleamate and formate. Maleamate was oxidized with liberation
of ammonia and maleate. In the presence of 10 mM meso-tartrate,
maleamate maleate were converted stoichiometrically into
fumarate (Orpin et al., 1971; Orpin, 1971a and 1972a).

In solution, diquat was rapidly degraded by sunlight or filtered
radiation from a mercury vapor lamp. As many as nine products,
many of a transient nature, were observed. Two possible photo-
chemical degradation pathways were suggested. The minor route
gave rise to the two pyridones IV and V. These in turn underwent
degradation to volatile fragments after prolonged irradiation.
The major route gave rise sequentially to compounds II, III, and
VI. The latter then also underwent degradation to volatile fragments.
The pyridone VII has also been detected (Smith and Grove, 1969).

Washed suspensions of Achromobacter D utilized the 4-carboxy-
1-methylpyridinium (MINA) moiety from paraquat degradation and
released methylamine from the N-methyl portion of the molecule.
With supplements of NAD^+ or NADH, cell-free extracts catalyzed
the evolution of CO_2 from the pyridinium carboxy group. The
remaining five carbon atoms gave rise to formate and succinate.
Formate formed from C-2 and succinate from C-3 to C-6. Hydroxy-
lation did not seem to be involved in this metabolism. The studies
indicated direct oxidative fission of a partly reduced ring to form

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Diquat(I)

(VII)

Minor

Major

(IV)

+

(V)

(VI)

(II)
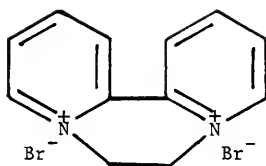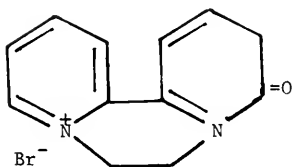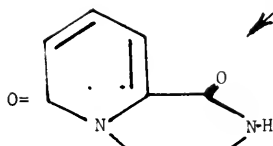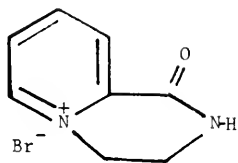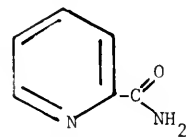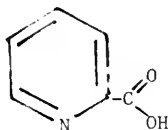
(III)

VOLATILE FRAGMENTS

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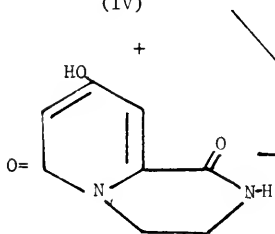
a dialdehyde. Hydrolysis would then release formate and methyl-
amine and produce succinic dialdehyde. Oxidation of the latter
through the semialdehyde to succinate was also indicated by the
studies. Oxidation appeared to be via N-methyl-1,4-dihydroiso-
nicotinate, γ-(N-formyl-N-methylamino)vinylacetaldehyde, γ-(N-
methylamino)vinylacetaldehyde, the corresponding acetate, and
succinic semialdehyde (Cain et al., 1970; Wright and Cain, 1969,
1970, 1972a and 1972b).

Streptomyces sp., Nocardia sp., and nine actinomycetal isolates
decomposed paraquat. Chromatography indicated the presence of
the 1-methyl-4-carboxypyridylium ion (Namdeo, 1972).

Two bacteria isolated were capable of oxidizing N-methyliso-
nicotinate. With strain 4C1 (a gram-positive bacterium), the first
step appeared to be hydroxylation at C-2. Although the 2-hydroxy
compound was not demonstrated enzymically, it was oxidized without
lag by whole cells. The 2-hydroxy compound probably served as the
substrate for demethylation with the methyl group being converted
to formaldehyde. 2-Hydroxyisonicotinate was hydroxylated to the 2,6-
dihydroxy analog by crude cell-free extracts. Cell-free extracts also
deamidated maleamate to maleate which gave rise to formaldehyde and
fumarate.

Cell-free extracts of 4C2 (a gram=negative rod bacterium) oxidized
N-methylisonicotinate, succinate, succinic semialdehyde, methyl-
amine,formaldehyde, and formate without lag.2-Hydroxy-N-methyl-
isonicotinate was not oxidized nor were mono- and dihydroxy-
pyridines. The observations with strain 4C2 were similar to those
previously observed with Achromobacter D. N-Methylisonicotinate was
partially reduced and thering opened by an oxygenase. Ring nitrogen
was then released as methylamine. Strain 4C2 oxidized the methylamine
via formaldehyde and formate to CO_2. Achromobacter D did not oxidize
methylamine (Cain et al., 1970; Orpin et al., 1972b).

Asecond pathway for bacterial degradation of N-methylisonicotinate
was observed in a gram-positive rod, isolated from soil, which was
capable of utilizing this product as a sole carbon source. Incubation

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of whole cells with N-[^{14}C]-methylisonicotinate released more than
50% of the label as ^{14}C-formaldehyde. No labeled methylamine was
detected. When Whole cells were incubated with ^{14}C-carboxy **N-methyl-**
isonicotinate, 95% of the label appeared as ^{14}CO$_2$. Whole cells grown
on N-methylisonicotinate were capable of immediate oxidation of the
2-hydroxy analog. Although crude cell-free extracts could not
oxidize N-methylisonicotinate or its 2-hydroxy analog, 2-hydroxy-
isonicotinate was rapidly oxidized to 2,6-dihydroxyisonicotinate.
The data suggested that the first step in the pathway was hydroxy-
lation to 2-hydroxy-N-methylisonicotinate. This is demethylated with
release of the methyl group as formaldehyde. A second hydroxylation
produces 2,6-dihydroxyisonicotinate (Orpin et al., 1971b).

When buffered aqueous paraquat dichloride solution was subjectd
to flash photolysis in an inert atmosphere, transient formation
of the radicals PQ·$^+$ and Cl·$^-$ were observed. Additional products
were noted but not identified (McKellar and Turner, 1971).

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<u>Disulfiram</u> (TTD, Tetraethylthiuram disulfide) [Bis(<u>N</u>,<u>N</u>-diethylthio-
carbamoyl)disulfide]

In rats, disulfiram was metabolized to diethyldithiocarbamic acid
methyl ester (DDC-Me). This, in turn was capable of conversion to
glucuronic acid conjugation and other metabolites after S-demethyla-
tion. This methyl mercaptan was probably the source of the observed
sulfate. Similar <u>in vitro</u> observations were made (Gessner and
Jakubowski, 1972)

$$\begin{array}{c}C_2H_5 \\ C_2H_5\end{array}N\!-\!\overset{\overset{\displaystyle S}{\|}}{C}\!-\!S\!-\!S\!-\!\overset{\overset{\displaystyle S}{\|}}{C}\!-\!N\begin{array}{c}C_2H_5 \\ C_2H_5\end{array}$$

Disulfiram

$$\begin{array}{c}C_2H_5 \\ C_2H_5\end{array}N\!-\!\underset{\underset{\displaystyle S}{\|}}{C}\!-\!SH$$

$$\begin{array}{c}C_2H_5 \\ C_2H_5\end{array}NH \;+\; CS_2$$

$$\begin{array}{c}C_2H_5 \\ C_2H_5\end{array}N\!-\!\overset{\overset{\displaystyle S}{\|}}{C}\!-\!S\!-\!Glucuronide$$

$$\begin{array}{c}C_2H_5 \\ C_2H_5\end{array}N\!-\!\overset{\overset{\displaystyle S}{\|}}{C}\!-\!S\!-\!CH_3$$

$$\begin{array}{c}C_2H_5 \\ C_2H_5\end{array}N\!-\!\overset{\overset{\displaystyle S}{\|}}{C}\!-\!OH$$

Glucuronide

$HS\!-\!CH_3$ $SO_4^=$

HCHO

Other Metabolites

177
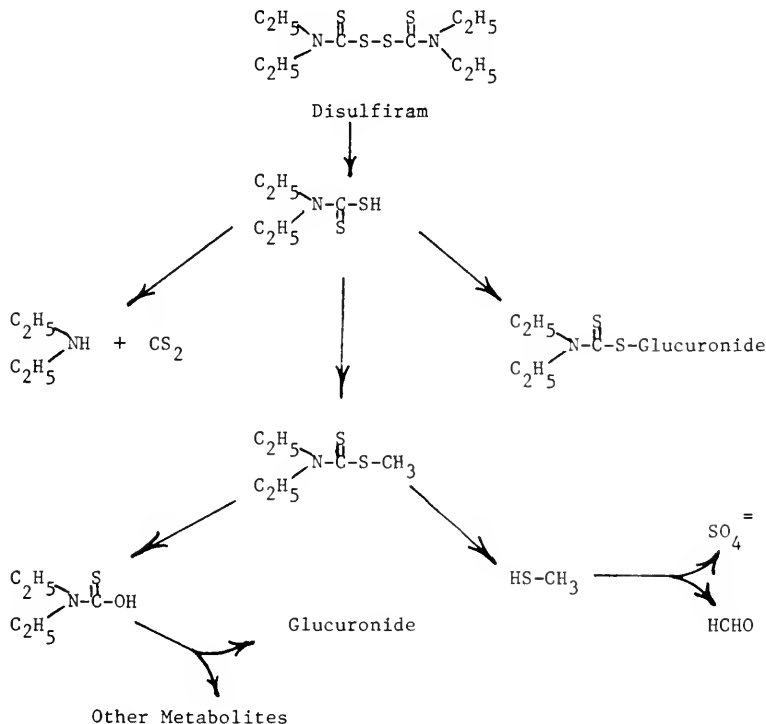
<u>Disulfoton</u> (Di-syston, dithiosystox, thiodemeton) [O,O-Diethyl-S-
(2-ethylthioethyl)phosphorodithioate]

Commercial fertilizers were impregnated with disulfoton. On the
fertilizer ingredients superphosphate and ammonium nitrate, all but
a trace of disulfoton was oxidized to the sulfone and sulfoxide.
Hydrolysis accounted for significant breakdown in several fertilizers
as well. On triple superphosphate and most other materials,
di-syston was relatively stable (Ibrahim et al., 1969).

Disulfoton was subjected to γ-radiation from ^{60}Co. Decomposition
was reduced at lower temperatures; increased with increasing
doses of radiation; and was greater in hexane and acetone than in
water. The sulfone, oxygen analog sulfone, and oxygen analog
sulfoxide were present (Grant et al., 1969).

Dithiocarbamates

Recent studies, based primarily on mass, Raman and NMR spectral data, have intidated a need to revise our conception of the structure of ethylene thiuram monosulfide (ETM). The data indicated that a better representation would be 5,6-dihydro-3H-imidaza[2,1-c]-1,2,4-dithiazole-3-thione (Benson et al., 1972; Pluijgers et al., 1971).

Spectrophotometric studies showed that ETU was a transformation product of EDI in water, especially at higher pH values (Habrekke and Goksyer, 1970). Photochemical degradation of ETU occurred also, after adsorption on a solid surface or in aquerous solution, when exposed to light and air (Cruickshank and Jarrow, 1972).

Cucumber and wheat seedlings were treated with ethylenethiourea, which is known to be present in plants after root treatment with ethylene bis-dithiocarbamate fungicides. Analysis of extracts of the treated seedlings indicated the presence of 2-imidazoline (Vonk and Sijpesteijn, 1971b).

CH_2-NCS
CH_2-NCS

EDI

CH_2-NH
CH_2-NH $C=S$

ETU

CH_2 — N — $C=S$
CH_2 — C — S
N — S

ETM

179
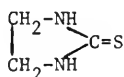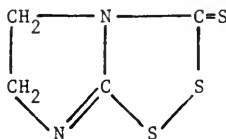
<u>Nabam</u> [Disodium ethylenebisdithiocarbamate]

Cucumber seedlings were treated with nabam via the roots. Sap pressed from the seedlings was chromatographed. The spot that appeared after development was chromatographically indistinguishable from ETU. This could, however, have been taken up from the solution in which it may form spontaneously.

After cucumber or wheat seedlings were allowed to take up ETU, the sap was pressed from them and analyzed by TLC. In addition to ETU, which was translocated to untreated parts of the plants, a **second** compound was observed but not identified. Tests did indicate that it was not ethyleneurea. The unknown material was also formed after incubation of ETU with sap of cucumber or tomato plants for a few hours. In water nabam breaks down rapidly to produce ETM and sulfur (Vonk and Sijpesteijn, 1970).

<u>Maneb</u> [Manganese ethylenebisdithiocarbamate]

<u>Zineb</u> [Zinc ethylenebisdithiocarbamate]

The fate of maneb and zineb does not differ markedly from that of nabam(Vonk and Sijpesteijn, 1970).
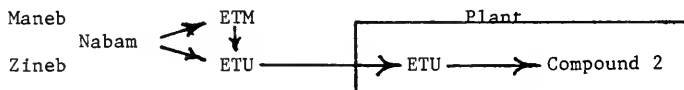
The degradation of maneb and zineb on surfaces was studied. Analyses, predominantly by chromatography, showed the presence of ethylenebis-thiourea, ethylenebisthiuram monosulfide, ethylenebisthiuram disulfide, ethylenediisothiocyanate, ethylenediamine, and sulfur (Engst and Schnaak, 1970).

After rats were administered maneb, feces and urine contained ethylene-diamine, ethylenebisthiuram monosulfide, ethylene thiourea and other unidentified metabolites (Seidler et al., 1970).

$$CH_2-N-C-S^- \quad \xrightarrow{-CS_2} \quad CH_2-NH_2 \quad \xrightarrow{-CS_2} \quad CH_2-NH_2$$

Ethylenebis-
dithicarbamate

Ethylene-
diamine

Oxidation

$-H_2S$

$-H_2S$

Ethylenebis-
thiuramdisulfide

Ethylenebis-
thiuram mono-
sulfide
(ETM)

$-S$

$-CS_2$

$-H_2S$

$-CS_2$
&
$-S$

$$CH_2-N=C=S$$
$$CH_2-N=C=S$$

Ethylenedi-
isothiocyanate
(EDI)

$$CH_2-N$$
$$\qquad C=S$$
$$CH_2-N$$

Ethylenethiourea
(ETU)

In studies with potassium and zinc dimethyldithiocarbamates, volatile products were formed from residues on higher plants. Significant‧ amounts of carbon disulfide were released. This reaction could occur on leaf surfaces where the approximate pH=5.7 is probably due in part to the dissolved CO_2. The other product of acidic decomposition, trimethylammonium bicarbonate, would be unstable. This would decompose to trimethylamine. Only small amounts of trimethylamine were observed. No methylisothiocyanate or H_2S was detected (Hylin and Chin, 1968).

$$R_1 \underset{R_1}{\overset{R}{N}}-\overset{S}{\underset{\parallel}{C}}-S^- \underset{\overline{}}{\overset{K_1}{\longleftrightarrow}} R_1 \underset{R_1}{\overset{R}{N}}-\overset{H-S}{\underset{\diagdown S}{C}} \underset{\overline{}}{\overset{k}{\longleftrightarrow}} R_1 \underset{R_1}{\overset{R}{N}}-\overset{H-S}{\underset{S}{C}} \longrightarrow \underset{R_1}{\overset{R}{N}}H + CS_2$$
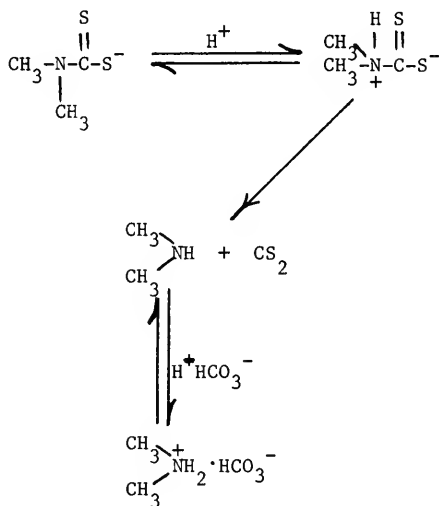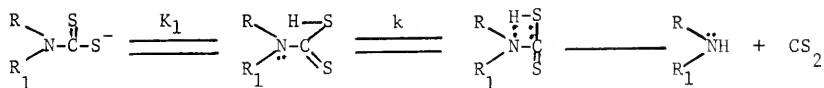
<u>Dithiocarbamates</u>

R	k min^{-1}	$pK_1 1$	pKa (R-NH$_2$)
	1.8×10^{-1}	1.6_3	8.25
	6.12×10^{-2} 7.59×10^{-2}	2.5_4	9.35
CH_3-CH_2—	3.32×10^{-2} 1.7×10^{-2}	3.2_6	10.63
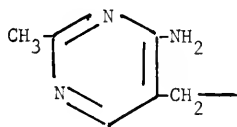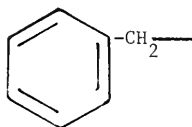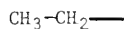
(Takami et al., 1972).

DNBP   (Dinoseb)   [2-sec-Butyl-4,6-dinitrophenol]

After incubation of DNBP with rumen fluid, 6-amino-2-butyl-4-
nitrophenol (ABNP) was observed. With continued incubation,
the concentration of ABNP diminished and that of 2-sec-butyl-
4,6-diaminophenol (BDAP) increased. When DNBP was administered
to cows, the same metabolites were observed as with the in vitro
studies (Froslie and Karlog, 1970).

DNOC [4,6-Dinitro-<u>o</u>-cresol]

Isolated sheep rumen contents rapidly reduced DNOC to 6-amino-4-
nitro-<u>o</u>-cresol and then to 4,6-diamino-<u>o</u>-cresol. Separation of
rumen contents, revealed that this reducing ability was shared
by protozoa and bacteria alike. Under normal conditions, no
conjugation was effected (Jegatheeswaran and Harvey, 1970).

When incubated with cow rumen fluid, DNOC could only be recovered
during the first 15 minutes. After about 10 minutes, there was
an increasing amount of 6-amino-4-nitro-<u>o</u>-cresol (6-ANOC). At
the end of 30 minutes, this began decreasing and could not be
detected after about 2 hours. One hour after the start of incu-
bation, a compound was observed that had an R_f= value and color
resembling that of 2-methyl-4,6-diaminophenol (DAOC). Another
spot was observed on the chromatogram but not identified. It
was seen after administration of DNOC or 6-ANOC. It was felt
that this was an intermediate formed during the conversion of
6-ANOC to DAOC. Similar results were obtained when DNOC was
administered to a cow (Froslie and Karlog, 1970).

In broth containing 250 ppm DNOC, <u>R</u>. <u>meliloti</u>, <u>R</u>. <u>trifolii</u>,
<u>R</u>. <u>leguminosarum</u> and <u>R</u>. <u>phaseoli</u> grew well. Other strains,
grew in broths containing lesser concentrations of DNOC. When
<u>R</u>. <u>leguminosarum</u> was used, five degradation products were
observed but only 3-amino-5-nitro-<u>o</u>-cresol was identified (Hamdi
and Tewfik, 1970).

<u>DRAZOXOLON</u> [4-[(2-chlorophenyl)hydrazono]-3-methyl-5-isoxazolone]

About 70 soil bacterial isolates were found capable of degrading
drazoxolon. An <u>Aerobacter</u> <u>cloacae</u>-like organism and a non-
fluorescent <u>Pseudomonas</u> sp. degraded drazoxolone preferentially
in neutral to alkaline media and were able to use the compound
as a sole nitrogen source. Two metabolites were identified as
2-(2-chlorophenylhydrazono)-acetoacetate and o-chloroaniline
(Anderson and Horsgood).

Drazoxolon

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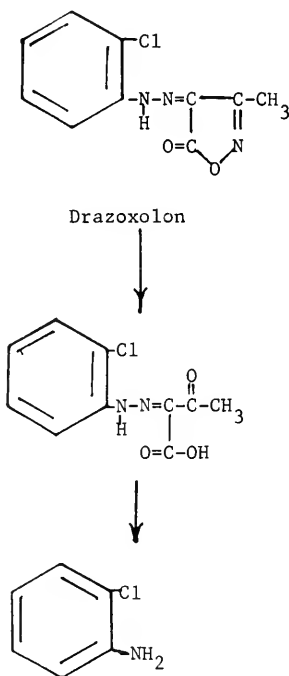
DYFONATE [O-Ethyl-S-phenyl ethylphosphonodithioate]

Dyfonate in oil was administered orally to albino rats. Rapid
metabolism of the material produced polar products which were
excreted in urine and feces. Metabolites isolated from urine
and identified were dyfonate oxon, O-ethyl O-methyl ethylphosphonate,
methylphenyl sulfoxide and sulfone, O-ethyl ethylphosphonothioic
acid, O-ethyl ethylphosphonic acid and the 3-hydroxy- and 4-hydroxy-
phenyl sulfones. Other unidentified materials, some conjugated,
were also detected. (Hoffman et al., 1971; McBain et al., 1971a).

Dyfonate was incubated with microsomes prepared from rat livers.
TLC and GLC analyses supported the identification of the oxon,
EOP, ETP and thiophenol as the major microsome metabolites.
Formation of ETP and the oxon required the presence of $NADPH_2$.
Use of oxygen isotopes demonstrated that the oxygen of the oxon
originated from molecular oxygen but that of ETP came only from
water, indicating formation of a common intermediate (McBain et al.,
1971b and 1971e).

When dyfonate was reacted with m-chloroperbenzoic acid in dichloro-
methane or incubated with the hepatic microsomal mixed-function
oxidase system, the same end products were formed. This indicated
that the same intermediate(s) may be involved. One intermediate
was isolated from the peracid oxidation. The reactions and spectral
characteristics of the oxygenated dyfonate were explained by a
resonance hybrid or rapidly equilibrating tautomeric mixture repre-
sented for convenience by Form II. Formation of the oxygenated
dyfonate and its subsequent hydrolysis explained formation of ETP,
EOP and thiophenol; but it did not explain formation of the oxon.
An unknown compound observed appeared to be an oxygenated precursor
to the oxon, ETO and EOP (McBain et al., 1971c and 1971d).

Potato plants were grown in soil treated with dyfonate. In addition
to unchanged dyfonate, seven metabolites were identified: oxon,
EOP, EOP-CH$_3$, ETP-CH$_3$, and some unknowns. The water-soluble
metabolites included EOP, ETP, MPSO$_2$ and several unknowns of which
49% gave rise to EOP when subjected to acid hydrolysis. Two
unknown materials were cleaved by β-glucosidase or glusulase but
less by β-glucuronidase. This suggested that the two metabolites
existed in the plant largely as glycoside and sulfate conjugates
(McBain et al., 1970).

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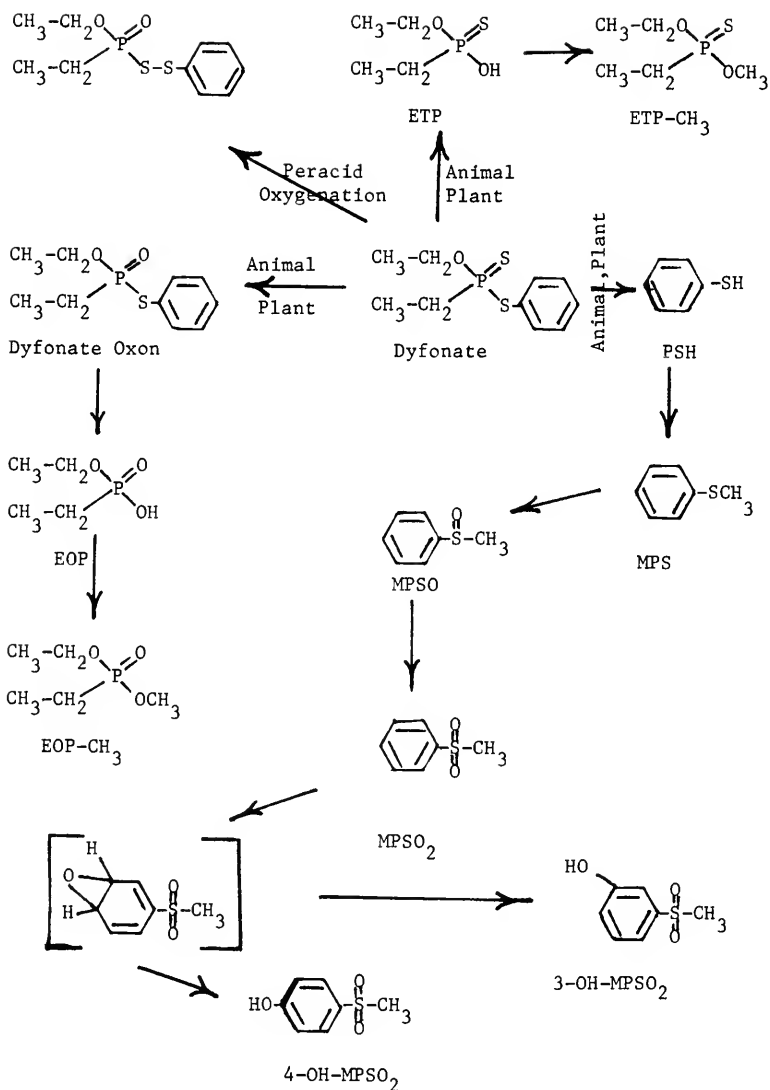
Loss of dyfonate from dyfonate-treated soil was greater when the labeling was on the ethoxy group than when the ring was labeled. From this it appeared that loss of dyfonate occurred by volatilization of the ethoxy moiety after degradation (Lichtenstein et al., 1972).

The reaction of dyfonate with m-chloroperbenzoic acid produced phenyl ethoxy ethylphosphinyl disulfide. By disulfide cleavage, this gave rise to ETP and phenyl mercaptan. Some elemental sulfur was also detected (Wustner et al., 1972).
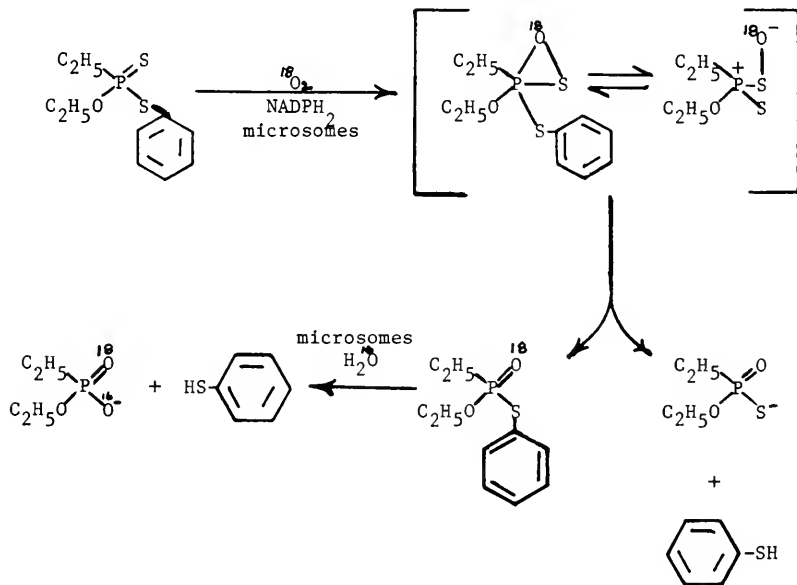
The residue and metabolic fate of labeled Elsan in cabbage seedling, strawberry, and apple fruit were studied. Elsan degraded rapidly in the plants and was hydrolyzed to non-toxic derivatives. The main metabolites found were Elsan carboxy derivatives, mandelic acid, and bis(carbethoxybenzyl)disulfide (Hayashi, 1972).
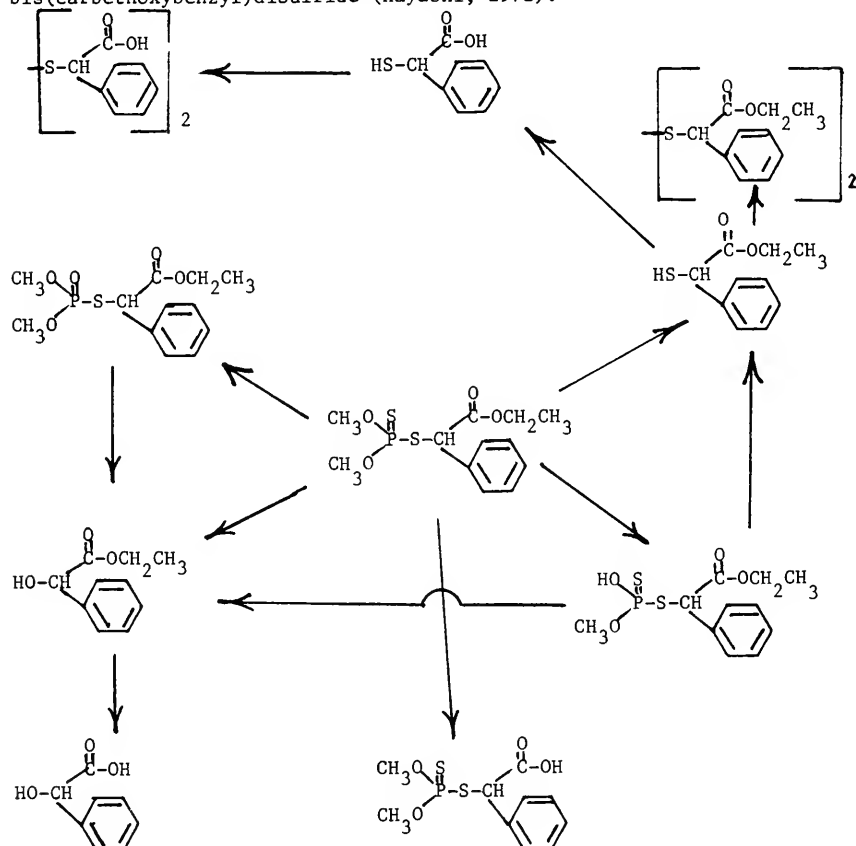
<u>ENDOSULFAN</u> (Thiodan) [6,7,8,9,10,10-Hexachloro-1,5,5a,6,9,9a-
            hexahydro-6,9-methano-2,4,3-benzodioxathiepin-3-oxide]

The diol analog of endosulfan was the major product produced by
UV irradiation of both endosulfan isomers. In addition to the
diol, endosulfan α-hydroxy ether, lactone, ether and unknown 1
were produced. Irradiation of the diol produced the α-hydroxy
ether and two unknowns 2 and 3. Irradiation of the ether gave
the α-hydroxy ether and the lactone. Irradiation of the α-hydroxy
ether gave the ether and unknowns 2 and 3. Irradiation of the
lactone gave small amounts (less than 1%) each of the diol and
ether (Archer et al., 1972). Ultraviolet irradiation of endosulfan
also produced two monodechlorinated products (Schumacher et al., 1971).

The dissipation of endosulfan was found to be dependent on substrate:
glass > sugar beets > beans; and from glass and plant surfaces:
ether > endosulfan II > sulfate > diol under a controlled environ-
ment. In the greenhouse, where conditions were semi-controlled,
loss from plant surfaces was: endosulfan I > ether > endosulfan II >
diol > sulfate. Metabolism was greater under greenhouse conditions.
The only metabolite observed was the sulfate. Under controlled
conditions, the sulfate and ether were detected (Beard and Water, 1969).

Endosulfan was applied three times at the rate of 0.5 and 1.5
lb/acre to field tobacco. Maximum time to zero residue level was
estimated to be ten days (Keil et al., 1971).

<u>ALODAN</u> (Chlorobicyclen, Hercules 426) [1,2,3,4,7,7-Hexachloro-5,6-
        di(chloromethyl)bicyclo[2.2.1]hept-2-ene]

Flies metabolized alodan through the cyclic derivative of an acid
and aldehyde (Ruckert and Ballschmiter, 1972).

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α −Endosulfan (I)   β−Endosulfan (II)

Endosulfan   Endosulfan sulfate   Endosulfan lactone

Endosulfan diol   Endosulfan hydroxyether
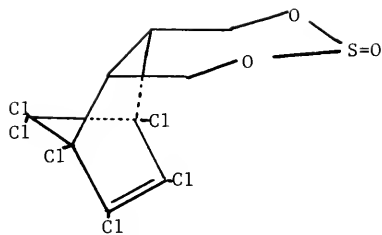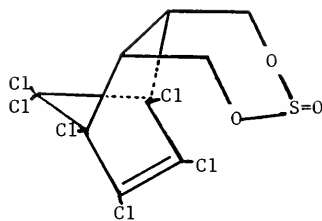
Endosulfan ether
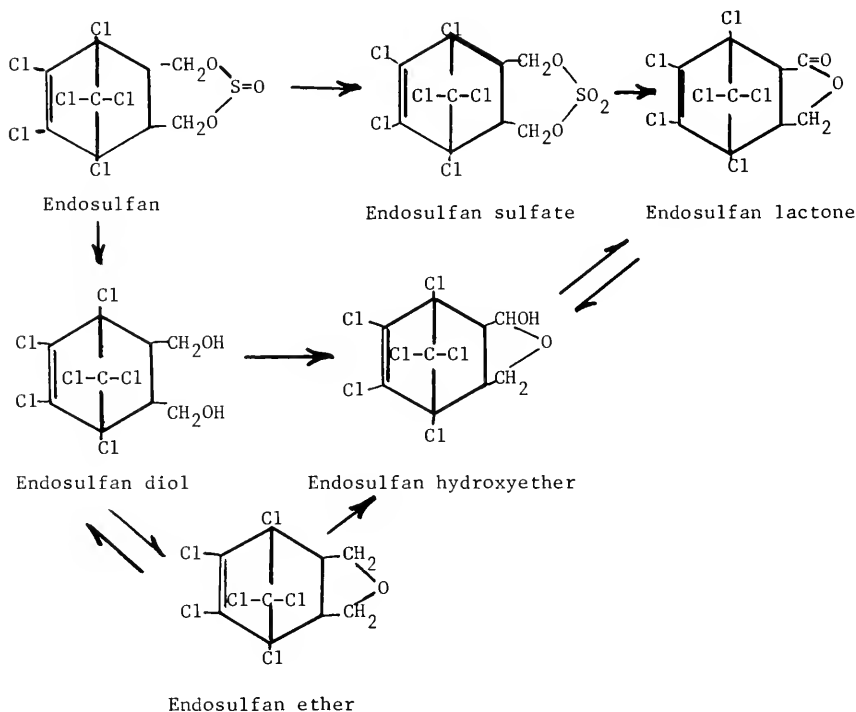
<u>ENDOTHALL</u> [7-Oxabicyclo(2.2.1)heptane-2,3-dicarboxylic acid]

^{14}C-Endothall, labeled at positions 1 and 2 of the ring, was added
to a pond water sample and to hydrosoil. Within ten days, 25%
of label was evolved as $^{14}CO_2$. An <u>arthrobacter</u> sp. isolated from
hydrosoil was able to utilize endothall as a sole source of carbon
for its growth. Label appeared incorporated into glutamic, aspartic
and citric acids and an unknown compound (Sikka, 1972).

<u>ETHIRIMOL</u> [5-Butyl-2-ethylamino-4-hydroxy-6-methylpyrimidine]

In the rat, ethirimol was metabolized via <u>N</u>-dealkylation, hydroxylation, and formation of the glucuronide (Calderbank, 1971).

When fed to barley plants via the roots, ethirimol had a half-life of 3-4 days. In addition to unchanged ethirimol, the <u>N</u>-dealkylated analog and a mixture of water-soluble products were found. After mild hydrolysis of the water-soluble material, four products were identified as ethirimol, desethyl ethirimol, ethirimol glucoside, and hydroxylated butyl ethirimol. Three other compounds were unidentified. The presence of the glucoside suggested the original presence of ethirimol glucopyranoside phosphate (Calderbank, 1971).

N-Ethyl-2-phenylcarbamoyloxy propionamide, D-isomer (11.561 R.P.)

This material disappeared rapidly from susceptible plant species,
whereas resistant plants accumulated it. Aniline appeared in
small amounts soon after treatment but was rapidly eliminated
(Desmoras et al., 1967).

Ethylene bromohydrin (EBH)

EBH was produced in wheat or flour by treatment with ethylene oxide
vapor and persisted in conditions of limited air movement. Flour
acidity changed from pH 5.6 to a maximum of 6.5 (Heuser and Scudamore,
1969).

Propylene oxide

When foods were treated with propylene oxide, 1-chloro-2-propanol
was found (Ragelis et al., 1968).

ETHYLENE OXIDE

Foodstuffs such as flour may acquire bromine from naturally
occurring inorganic bromide or from prior fumigation with
methylbromide. It is postulated that, as with chloride in the
presence of water, bromide too gives rise to acid which may
then react with the ethylene oxide to form the bromohydrin.
In wheat and wheat flour, ethylene bromohydrin has been observed
after fumigation with ethylene oxide (Heuser and Scudamore, 1969).

After fumigation and sterilization of foodstuffs with EO,
residues of unchanged EO remained. In most cases these residues
were rapidly lost by chemical reactions with commodity constituents
and by volatilization. Halohydrins and glycols and smaller
amounts of diethylene glycol were formed (Scudamore and Heuser, 1971).
2-Chloroethanol has been identified (Ragelis et al., 1968).

Exposure to ETO destroyed about 40% of the thiamine in a stock diet.
Similarly exposure of riboflavin, pyridoxine, niacin and folic acid
suspended in starch with choline chloride resulted in destruction
of practically all of the vitamins (Bakerman et al., 1956). When
dried prunes were fumigated with ^{14}C-labeled ethylene oxide, non-
volatile and relatively non-toxic alkylation products formed. More
than 50% of the label appeared as hydroxyethyl cellulose in the skin;
30%, as hydroxyethyl sugars in the pulp; and 3%, as glycols. The
remainder of the label has been tentatively identified as hydroxy-
ethylated amino acids and proteins (Gordon et al., 1959).

FENAC [2,3,6-Trichloroacetic acid]

Fenac was fed to a Holstein cow at 5 ppm in the diet for four days. Analysis of urine samples revealed the presence of herbicide representing 52.8% conjugated and 18.6% free acid of the total herbicide dose. No fenac was present in milk and feces samples. When incubated with rumen fluid or the 100000 xg supernatant faction of beef liver, fenac was not degraded (St. John and Lisk, 1970).

Irradiation of sodium fenac in aqueous solution gave rise to a complex mixture. The principal product was 2,5-dichlorobenzyl alcohol. Two other compounds were identified as trichloro- and dichloro-benzaldehyde (Crosby and Leitis, 1969).

FENAZAFLOR (Fenoflurazole, NC 5016) [Phenyl-5,6-dichloro-
                2-trifluoromethylbenzimidazole-1-carboxylate]

Mouse plasma and mouse liver homogenate catalyzed cleavage of
fenazaflor to 5,6-dichloro-2-trifluoromethylbenzimidazole
(5,6-Cl$_2$-TFB). In the presence of NADPH, the liver microsome
system converted 5,6-Cl$_2$-TFB to compounds suggestive of Cl-OH-
TFB. Methylation yielded two products which co-chromatographed
with the two isomers of N-methyl-4-methoxy-5,6-Cl$_2$-TFB. With
4,5-Cl$_2$-TFB, five compounds were observed and co-chromatographed
with isomers of N-Me-4,5-Cl$_2$-6-OMe-TFB,N-Me-4,5-Cl$_2$-7-OMe-TFB,
and N-Me-4,5-Cl$_2$-5-OMe-TFB, Microsomal mixed-function oxidases
converted 4,5-Cl$_2$-TFB to almost equal amounts of the 6-OH and
7-OH derivatives plus a small amount of the 5-OH analog. With
5,6-Cl$_2$-TFB, the 4-OH-5,6-Cl$_2$-TFB was formed. Other ether-
and water- soluble metabolites were formed but not identified
(Bowker and Casida, 1969).

Labeled fenazaflor and 5,6-Cl$_2$-TFB was administered orally to
rats and mice. The pattern of radiocarbon excretion from the
rats and mice was similar for both compounds. The same compounds
were observed, in almost the same proportions, in rats after the
oral administration of either compound. Those materials found
in rat urine only were: conjugate(s) of 5-Cl-6-OH-TFB, an uniden-
tified product, and unidentified conjugate(s); found in both rat
and mouse urine: N-glucuronide of 5,6-Cl$_2$-TFB; conjugates of
5-Cl-6-OH-TFB; 4-OH-5,6-Cl$_2$-TFB; 4,7-(OH)$_2$-5,6-Cl$_2$-TFB; conjugates
of hydroxy derivative(s) of 5,6-Cl$_2$-TFB. In urine of male rats,
after oral administration of 4,5-Cl$_2$-TFB, were the following:
conjugates of 4,5-Cl$_2$-6-OH-TFB, 4,5-Cl$_2$-7-OH-TFB, and 4,6-Cl$_2$-5-
OH-TFB; and 4,5-Cl$_2$-6-OH-TFB. Some additional metabolites were
not identified (Bowker and Casida, 1969).

After injection of 4,5- or 5,6-Cl$_2$-TFB into houseflies, 20-30%
of each was excreted as metabolites within 24 hours. One metabolite
was identified as the N-glucoside of 5,6-Cl$_2$-TFB; another was
tentatively identified as the N-flucoside of 4,5-Cl$_2$-TFB. A
third product was not identified (Bowker and Casida, 1969).

On apple fruit and leaves, fenazaflor breakdown yielded 5,6-Cl$_2$-
TFB, an unknown, N-glucoside of 4-OH-5,6-Cl$_2$-TFB and 4-O-glucoside
of 5,6-Cl$_2$-TFB (Bowker and Casida, 1969).

This acaricide was hydrolyzed in water to give 5,6-dichloro-2-
trifluoromethylbenzimidazole (Corbett and Wright, 1970).

A= Apples
B= Beans
E= Enzymatic in vitro
F= Houseflies
M= Mouse
R= Rat

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FENSULFOTHION (Dasanit, Terracur-P, Bay 25141) [O,O-Diethyl O-(p-
                methylsulfinylphenyl)phosphorothionate]

No residues of fensulfothion or its oxidation products were found
in fat, muscle, or liver of sheep after oral administration. After
application to pasture plots, in addition to unchanged fensulfo-
thion, fensulfothion sulfone and fensulfothion oxygen analog
sulfoxide and sulfone were also found (Solly and Harrison, 1971).
These studies also indicated that withholding sheep from grazing
on treated pasture for a period of one month would be sufficient
to avoid toxicity hazards to sheep and residues in derived food-
stuffs (Solly et al., 1971a).

Cows were grazed on pasture treated with fensulfothion. Milk
from cows allowed to graze 28 days later did not contain detectable
residues; but, in butterfat of cows that grazed 14 days after
treatment, traces (0.02 ppm) were detectable after 3 days of
grazing. The milk residues were in the form of fensulfothion
oxygen analog sulfone; on the pasture, it was mainly fensulfothion
sulfone (Solly et al., 1971b).

Coastal bermudagrass and forage corn were treated with fensulfothion.
After 28 days of weathering, total residues remaining on those plants
treated at 2.0 lb A were about 4 and 7 ppm (wet basis), respectively.
In addition to unchanged fensulfothion, the sulfone and the sulfoxide
and sulfone of the oxygen analog were also observed (Leuck and Bowman,
1972).

<u>FENTHION</u> [O,O-Dimethyl-O-(4-methylthio)-m-tolyl-phosphorothioate]

Larvae of resistant <u>Culex</u> <u>pipiens</u> <u>fatigans</u> Wied. absorbed half
as much fenthion as those non-resistant and degraded proportionately
twice as much to water-soluble metabolites. Oxonase activity
increased four fold in the resistant strain. Esterase activity
was also greater and could hydrolyze fenoxon.

Resistant and susceptible strain larvae showed three identical
peaks: dimethyl phosphoric acid; O,O-dimethyl phosphorothionic
acid; and an unidentified compound. Oxidative metabolites from
larval bodies were identified as fenoxon sulfoxide and sulfone
and in the exposure water as fenthion sulfoxide & fenoxon sulfoxide.
Differences between resistant and susceptible strains were quantita-
tive not qualitative (Stone & Brown, 1969).

Southern house mosquito larvae (<u>Culex</u> <u>pipiens</u> <u>quinquefasciatus</u> Say)
oxidized fenthion to fenoxon sulfoxide and fenoxon sulfone. In
the exposure water, fenthion sulfoxide and fenoxon sulfoxide were
found. When larvae were exposed to high concentrations of fenthion,
fenoxon was observed. In the larval bodies, dimethyl phosphate
and dimethyl phosphorothionate were also found. The latter product
was the most abundant, an indication of the importance of thionase-
type hydrolysis in fenthion detoxification by normal strains of this
mosquito (Stone, 1969).

Both the stable fly and the bed bug rapidly metabolized fenthion.
Oxidation occurred at the thiophosphoryl and thioether positions.
The latter path produced fenthion sulfoxide and fenthion sulfone.
The other path gave rise to fenoxon and 4-methylsulfonyl-m-cresol.
The sulfinyl cresol analog was also observed. The hydrolytic products
were conjugated and excreted. Following conversion to the oxygen
analog, oxidation of the thioether was more rapid (Young and Berger,
1969).

Fenthion was sprayed on 3 kinds of rice plants in different growth
stages. Disappearance was rapid and only about 10% of chloroform
extractable metabolites – primarily fenthion sulfoxide and sulfone –
remains as fenthion after 6 hours. Water-soluble metabolites in
rice grains after 14 days were identified as phosphoric acid,
phosphorothioic acid, O,O-dimethyl phosphoric acid, O,O-dimethyl
phosphorothioic acid and monodemethylated fenthion (Fukuda et al., 1962).

Lactating Jersey cows were fed diets containing fenthion. Milk contained traces of fenthion and small amounts of fenthion sulfoxide and sulfone and the sulfoxide of the oxygen analog. The sulfone and sulfoxide of fenthion and its oxygen analog were found in urine. Fenthion sulfoxide was found in feces (Johnson and Bowman, 1972).

<u>Fluoroacetate</u> [Fluoroacetic acid]

In lettuce, the only detected metabolite of fluoroacetate was <u>S</u>-car-
boxymethylglutathione (Ward and Huskisson, 1972).

FLUORODIFEN   (C-6989, Preforan)   [2,4'-dinitro-4-trifluoromethyl diphenyl ether]

Soybeans were grown in nutrient solution containing ^{14}C-labeled
C-6989. Thin-layer chromatography indicated the presence of
4-trifluoromethyl-2-amino-4'-nitrodiphenyl ether, the diamino
analog, and p-nitrophenol in roots and shoots. The data
indicated that metabolism of C-6989 in soybean was primarily by
ether cleavage (Rogers, 1971).

Cucumber seedlings were exposed to fluorodifen via nutrient
solution. One of the major degradation products was p-nitrophenol
and an unknown (probably a conjugate of p-nitrophenol). Also
observed were 2-aminofluorodifen, diaminofluorodifen, p-amino-
fluorodifen, 2-amino-4-trifluoromethylphenol, 2-nitro-4-trifluoro-
methylphenol and several unidentified compounds. The phenolic
metabolites were conjugated with plant constituents, probably
glucosides (Eastin, 1972).

Peanut seedlings (Arachis hypogaea) rapidly metabolized fluorodifen.
The major metabolism proceeded via ether hydrolysis and reduction
of the 4-nitrophenol to 4-aminophenol. A minor pathway proceeded via
reduction of a nitro group followed by ether cleavage. Both mono-
amino ethers were observed but no di-amino ether was detected. Two
other unidentified metabolites were detected (Eastin, 1969 and 1972b).

Preforan was incubated with tobacco cells. After 15 days, between
52 and 76% of the label was recovered. Between 60 and 80% of this
was incorporated into the cells. The metabolites were characterized
as conjugates of 4-nitrophenol. These included glucoside, amino
acid and/or protein conjugates (Locke and Baron, 1972).

Preforan was incubated with soil and with cultures of Talaromyces
wortmanii and a soil bacillus. The major chloroform-soluble was
the 2-amino derivative. Further degradation occurred by reduction,
ether cleavage and hydrolysis of the trifluoromethyl group. Some
metabolic products in soil were incorporated in humic acid fractions
(Ross and Tweedy, 1971).

A dry film of fluorodifen decomposed rapidly under UV (253.7 nm).
After 12 hours, p-nitrophenol, p-aminophenol and 2-nitro-4-
trifluoromethylphenol were present. After 48 hours, p-aminofluoro-
difen was also detected. Another unidentified compound also found
was the major photolysis product (Eastin, 1972a).

Fluorodifen

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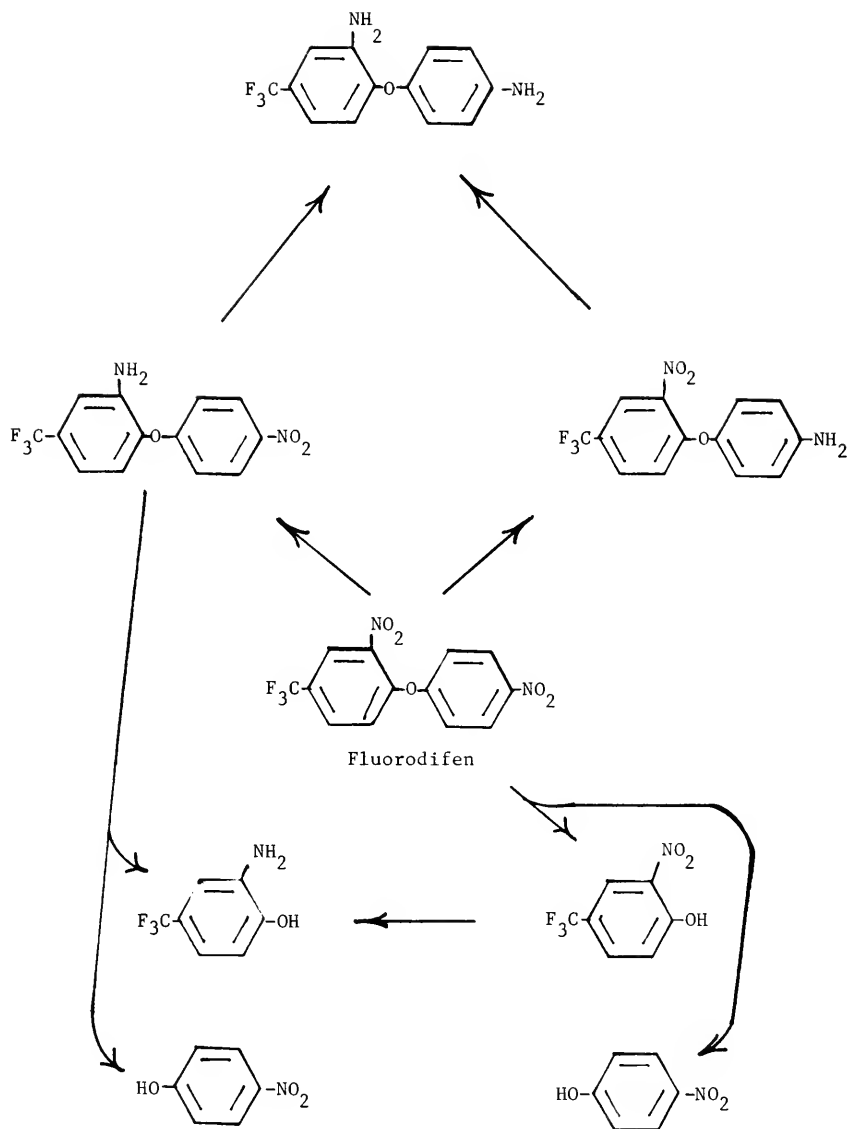
p-Fluorophenylacetic Acid
_____

A <u>Pseudomonas</u> sp., capable of growing on p-fluorophenylacetic
acid, was isolated. During growth, more than 85% of the fluorine
was released into the culture medium as fluoride ion. The main
degradative products were identified as <u>trans</u>-3-fluoro-3-hexene-
dioic acid, (-)4-carboxymethyl-4-fluorobutanolide, 4-fluoro-3-
hydroxyphenylacetic acid, 4-fluoro-2-hydroxyphenylacetic acid,
and D(+) monofluorosuccinic acid. Organically bound fluorine
appeared to be eliminated as fluoride by the action of fumarase
on fluorofumarate. Oxaloacetate and hydrogen fluoride were
produced (Harper and Blakley, 1970 and 1971a).

Other studies have shown that 3-fluoro-3-hexenedioic acid was
lactonized to give the 4-fluorobutanolide. This may be hydrolyzed
to 3-hydroxy-3-fluoroadipic acid which spontaneously liberates
HF and forms β-ketoadipic acid. The hexenedioic acid may also
lactonize to form 3-fluorobutanolide, which is hydrolyzed to
3-keto-4-fluoroadipic acid and cleaved to form acetate and mono-
fluorosuccinic acid. This is converted to fluorofumaric acid and
then fluoromalic acid. The latter decomposes to oxaloacetate
and HF (Harper and Blakley, 1971b).

4-Carboxymethyl-
4-fluorobutanolide

3-Fluoro-3-
Hexenedioic acid

(-)-4-Carboxymethyl-3-fluoro-
butanolide

β-Ketoadipic acid

Co A

AcCo A
+

TCA Cycle

4-Fluoro-3-keto-
adipic acid

AcCo A
+

D(+)
Fluorosuccinic
acid

Fluorofumarate

HF

2-Fluoromalate

TCA Cycle

Oxaloacetate

HF
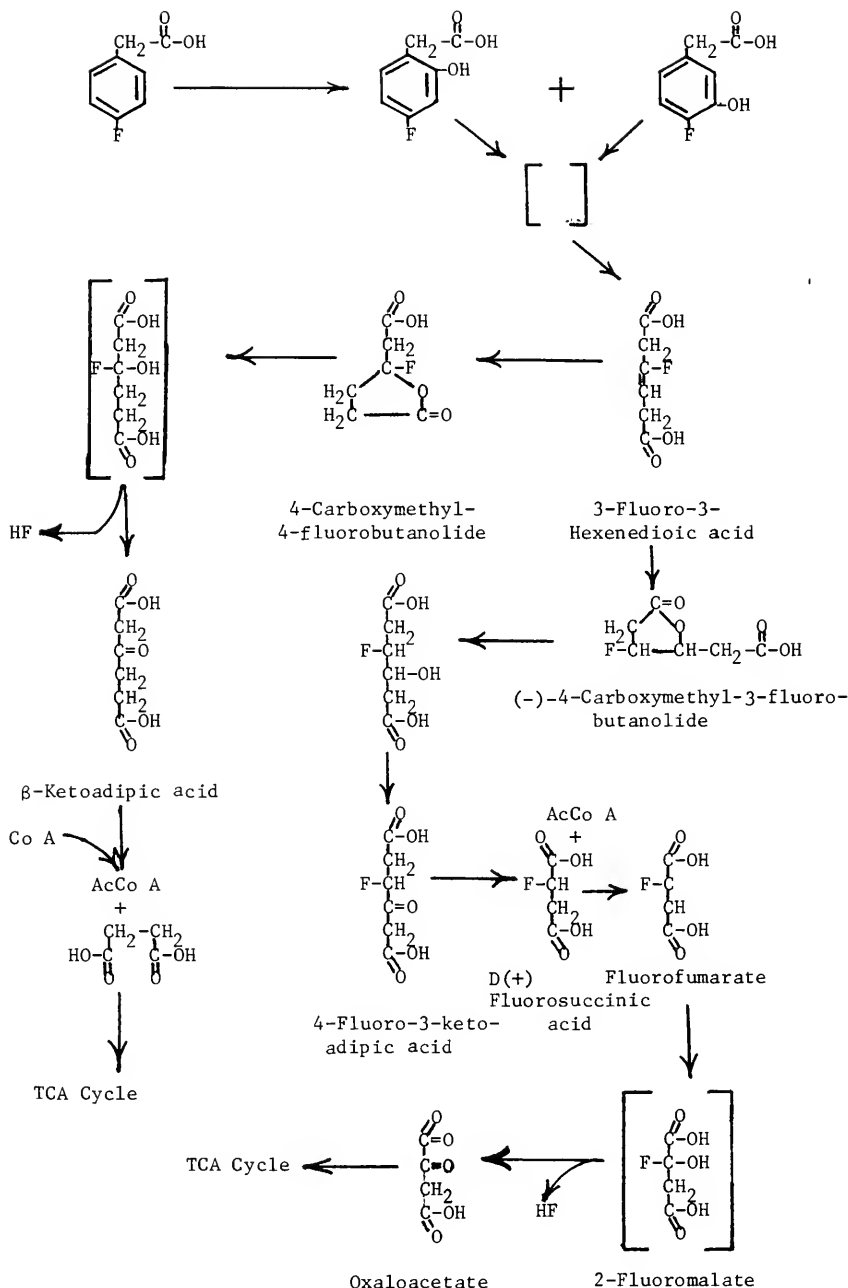
FLURENOL, BUTYL ESTER [n-Butyl 9-hydroxyfluorene-9-carboxylate]

[14]C-Labeled flurenol-n-butyl ester was applied to leaves of
Phaseolus vulgaris. Two glucosidic metabolites were characterized
as containing glucose and the 2'-hydroxy- and 3'-hydroxy-n-butyl
esters of flurenol. Two unstable metabolites were observed that
decomposed and yielded the characterized glucosides. Three more
polar metabolites appeared to be amino acid conjugates, one of which
contained a hydroxyl group on the aromatic portion of the molecule
(Wotschokowsky, 1972).
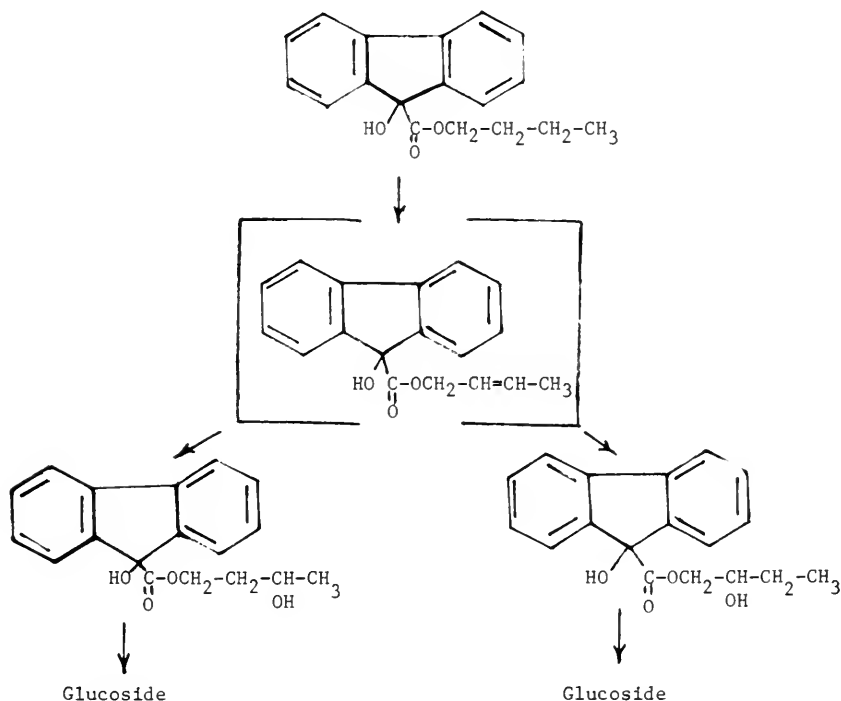
FORMETANATE (Carzol) [m-(Dimethylaminomethyleneimino)phenyl-
N-methylcarbamate]

Rats were orally administered formetanate (I). About 80% of
the dose was eliminated in the urine and 6% in the feces after
24 hours. Metabolites were isolated and identified by chromatography
as m-formaminophenyl-N-methylcarbamate (II), m-formaminophenol (IV),
m-aminophenol (V), m-acetamidophenol (VI), and glucuronide IX and
sulfate X of compound VI (Gupta and Knowles, 1970).

Soluble liver enzymes hydrolyzed m-formaminophenyl-N-methyl
carbamate (II) to m-aminophenol (V) and deformylated m-formamino-
phenol to m-aminophenol. The enzyme formamidase appeared to be
involved in these reactions (Ahmad and Knowles, 1970a and 1970b).

After injection into the stem of orange seedlings, formetanate
quickly translocated into the leaves. Metabolism by the seedlings
produced demethylformetanate (III), m-aminophenyl-N-methylcarbamate
(VIII), m-formaminophenyl-N-methylcarbamate free (II) and conjugated
(IIa), m-formaminophenol free (IV) and conjugated (IVa), m-amino-
phenol free (V) and conjugated (VI and VIa) and m-(dimethylamino-
methyleneimino)phenol (VII) (Knowles and Gupta, 1970).

River bottom soil samples were mixed with labeled formetanate and
incubated for up to 16 days. At that time, m-formaminophenol (IV)
was the metabolite present in greatest (58.5%) amount. Also
present were the ethylacetate soluble compounds II (7.8%), III
(1.2%),V (19.0%), and VII (1.9%) (Arurkar and Knowles, 1970).

This acaricide was irradiated in aqueous solution a λ> 286 nm.
Photoproducts, analyzed by mass and infrared spectrometry, were
identified as: m-formamidophenyl N-methylcarbamate (II); m-aminophenyl
N-methylcarbamate (VIII); m-formamidophenol (IV); and m-hydroxyphenyl
N-methylcarbamate (XI) (Su and Zabik, 1972b).

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R=Rat
L=Liver homogenate
P=Plant
I=Irradiation

211
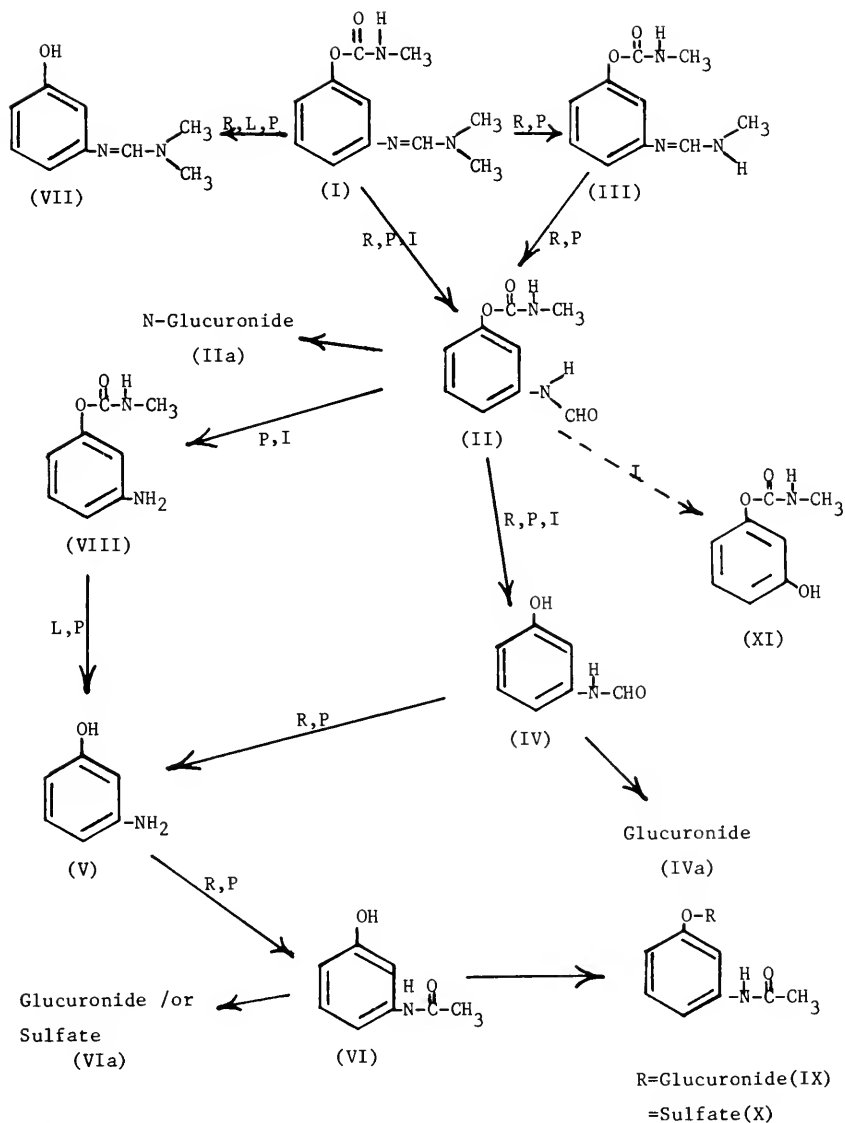
FORMOTHION (Anthio) [$\underline{O}$,$\underline{O}$-Dimethyl $\underline{S}$-($\underline{N}$-methyl $\underline{N}$-formylcarbamoylmethyl) phosphorodithioate]

The half-life of formothion breakdown after application to bean plants was 1.2 days. Hydrolysis caused rapid degradation to dimethoate and $\underline{O}$,$\underline{O}$-dimethyl dithiophosphorylacetic acid. Further degradation yielded dimethoxon, $\underline{O}$,$\underline{O}$-dimethyldithiophosphoric acid and bis($\underline{O}$,$\underline{O}$-dimethylthiophosphoryl)disulfide (Sauer, 1972).

See also DIMETHOATE.

$$(CH_3O)_2\text{-}\overset{S}{\overset{\|}{P}}\text{-S-CH}_2\text{-}\overset{O}{\overset{\|}{C}}\text{-N}\overset{CHO}{\underset{CH_3}{}}$$

Formothion

$$(CH_3O)_2\text{-}\overset{S}{\overset{\|}{P}}\text{-S-CH}_2\text{-}\overset{O}{\overset{\|}{C}}\text{-OH}$$

$$CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-OH}$$

$$[(CH_3O)_2\text{-}\overset{S}{\overset{\|}{P}}\text{-S}]_2$$

$$(CH_3O)_2\text{-}\overset{S}{\overset{\|}{P}}\text{-S-CH}_2\text{-}\overset{O}{\overset{\|}{C}}\text{-N}\overset{H}{\underset{CH_3}{}}$$

Dimethoate

$$(CH_3O)_2\text{-}\overset{S}{\overset{\|}{P}}\text{-SH}$$

$$(CH_3O)_2\text{-}\overset{O}{\overset{\|}{P}}\text{-S-CH}_2\text{-}\overset{O}{\overset{\|}{C}}\text{-N}\overset{H}{\underset{CH_3}{}}$$

Dimethoxon

212
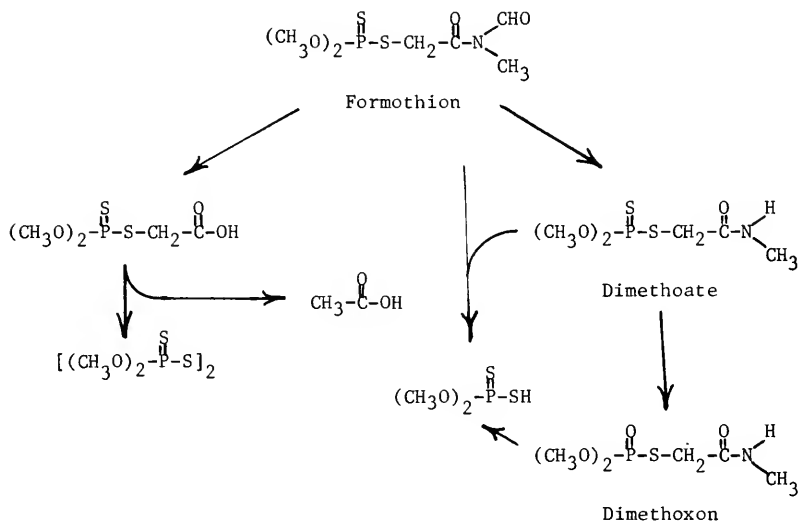
<u>FRESCON</u>   (Trifenmorph, Tritylmorpholine)   [<u>N</u>-Triphenylmethyl
          morpholine]

After turf was treated with Frescon, analyses indicated the presence
of five components. One component was hydrophilic and was hydrolyzed
by sulfuric acid to five unidentified compounds. Two other components,
which behaved as neutral compounds on paper electrophoresis at pH 10,
were converted by acid hydrolysis into triphenylcarbinol. Two other
components were identified as triphenylcarbinol and the parent com-
pound.

Half of the <u>N</u>-tritylmorpholine applied to soil was lost in 1 to 4
weeks. Triphenylcarbinol was detected in the soil(Beynon et al.,
1972).

<u>Gardona</u> (Tetrachlorvinphos, SD 8447) [2-Chloro-1-$(2^1,4^1,5^1$-trichloro-phenyl)vinyl dimethyl phosphate]

At a level of 5 ppm in the daily ration of a dairy cow, no gardona residues were found in milk or urine. However, after hydrolysis of urine, a metabolite was found that exhibited a retention time identical to that of 1-(2,4,5-trichlorophenyl) ethanol. The same metabolite was observed when gardona was incubated with a preparation from beef liver (Gutenmann et al., 1971).

Gardona, labeled at the methyl group, was incubated with gluta-thione and a hepatic microsomal oxidative system. Chromatography revealed all radioactivity coincided with S-methyl glutathione and the monodesmethyl metabolite (Hutson et al., 1968).

With the use of labeled material, the degradation of gardona was studied in plants - cabbage, apple foliage and fruit, and rice- and in soils under laboratory conditions. Some isomerization to the α-isomer occurred on the foliage and initial half-life of gardona was about 1 day. In soil, the half-life was about 4-5 days. Initial breakdown on plants and in soil was by hydrolysis to both demethyl gardona and to 2,4,5-trichlorophenacyl chloride (III). The major breakdown products were gylcoside conjugates of 1-(2,4,5-trichlorophenyl)ethan-1-ol (VI). The sugar moieties were probably galactose, mannose, or fructose and possibly a dissacharide. Some conjugation metabolites (III and V̇) were also observed. Combined residues of III, IV, V and VI on foliage did not exceed 5.3% of the applied dose (Beynon and Wright, 1969).

Mammalian liver supernatant protein (100,000G) demethylated gardona in the presence of glutathione. Glutathione acted as a methyl group acceptor and formed the S-methyl analog and the monodemethyl analog of gardona (Hutson et al., 1972).

(I)

Gardona
(β-Isomer)

P → α-Isomer

P,S

P,S

(II)

(III)

(V)

(VII)

Conjugates

P

Inorganic
Phosphate

(IV)

(VI)

Glycosides

P
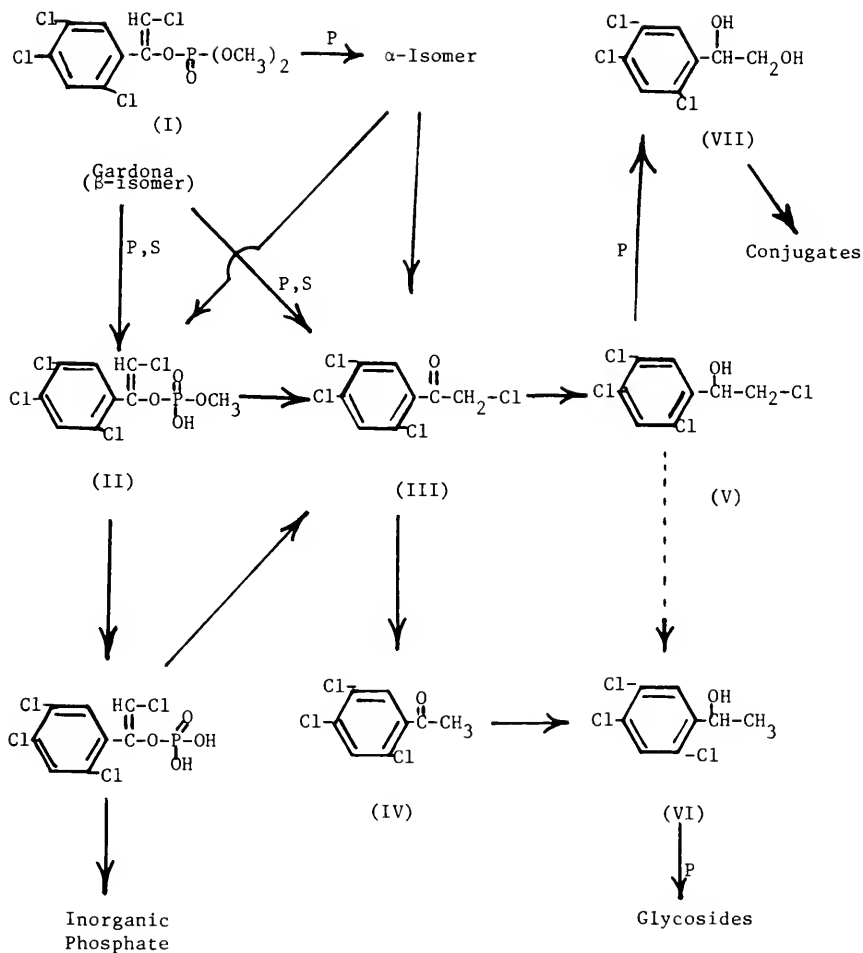
P=Plants
S=Soil

Griseofulvin [7-Chloro-4,6-dimethoxycoumaran-3-one-2-spiro-1^1-
(2^1-methoxy-6^1-methylcyclohex-2^1-en-4^1-one]

Mice were given oral doses of griseofulvin. After extraction and
chromatography, four peaks were observed: 4-desmethylgriseofulvin
(4-DM), 6-desmethylgriseofulvin (6-DM), and two unidentified compounds.
The 4-DM appeared free and in conjugated form (Lin et al., 1972).

GC-6506 [O,O-Dimethyl O-(4-methylthiophenyl) phosphate]

After intraperitioneal injection of ^{32}P-labeled GC-6506 into female white Sprague-Dawley rats, over 90% of the dose was excreted in the urine. Dimethyl phosphate was the predominant product. When rats were treated with ^{14}C-labeled GC-6506, about 82% of the dose was excreted in the urine within 16 hours. No ^{14}CO$_2$ was evolved as late as 24 hours post-treatment. No rupture of the C-S bond nor hydroxylation of the phenyl ring was detected. Other studies, with phenolsulfatase and β-glucuronidase, disclosed the presence of sulfuric and glucuronic acid conjugates of the substituted phenols (Bull & Stokes, 1970).

Studies of the metabolism of labeled GS-6506 and its oxidation products after oral administration to 5th instar tobacco budworms showed that the route was qualitatively the same as in plants. Initially approximately equivalent cleavage of O-methyl and P-O-phenyl linkages occurred. The O-demethylation was glutathione dependent; the P-O phenyl cleavage was associated with two enzymes. Studies with the phenol -SO$_2$ indicated that this material was converted into unidentified conjugates (Bull and Stokes, 1970).

In resistant and non-resistant fifth-instar tobacco budworms (Heliothis virescens F.), the sulfone metabolite was degraded by demethylation and rupture of the phenyl-phosphate bond. The substituted phenol resulting from the latter was rapidly conjugated as the glucoside. Both processes were more active in the resistant insects (Bull & Whitten, 1972).

Cotton leaves, treated with labeled GC-6506, converted the material to many metabolites. Enzyme studies showed the presence of phenol glucosides which in turn were altered to unknown compounds. Studies of other phenols in plants had shown the formation of β-gentiobioside. It is probable that similar compounds formed in these studies. The biological half-lives of GC-6506 and its oxidative derivatives inside the cotton plant did not exceed two days. Small concentrations of O-demethyl GC-6506-SO and -SO$_2$ were present as well as O-demethyl GC-6506 (Bull and Stokes, 1970; Wendell and Bull, 1970).

1=Rat
2=Plant
3=Insect

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<u>H-722</u> [3-(2'-Methylphenoxy)pyridazine]

After application of labeled H-722 to susceptible barley and
tolerant tomato plants, four metabolites were detected. Three
were identified as the 1-<u>N</u>-oxide, 3-keto analog, and the 3-glucosyl
derivative (Nakagawa et al., 1971).
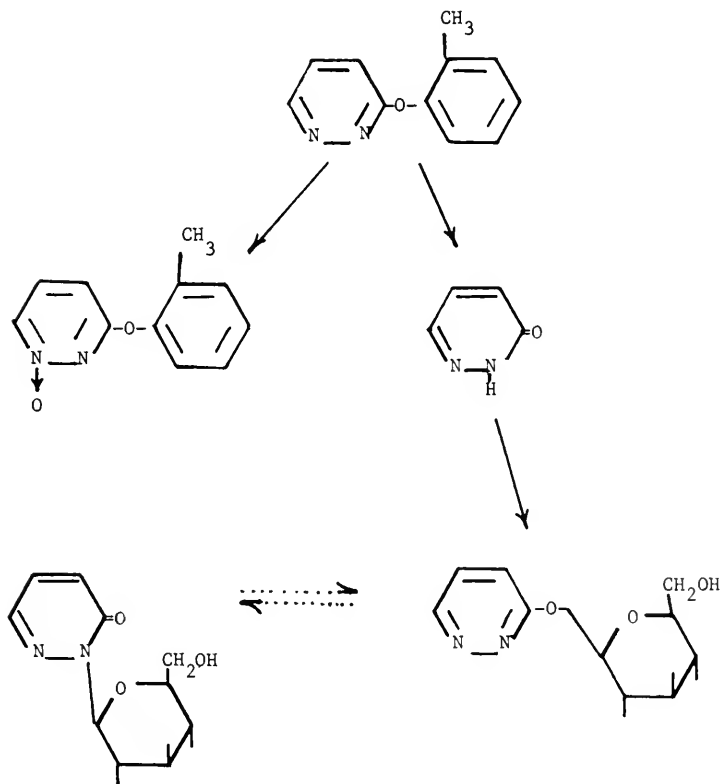
HERBISAN (Bexide) [Diethyl xanthogen]

Herbisan was fed to a lactating cow. Neither herbisan nor
diethyl xanthate, a possible metabolite, was detected in milk,
urine, or feces. Herbisan was not recovered in any form after
incubation with rumen fluid. There was no degradation to diethyl
xanthate (Gutemann and Lisk, 1971).

<u>HEXACHLOROPHENE</u> (Gamophen, Hexosan) [Bis(2-hydroxy-3,5,6-
                    trichlorophenyl) methane]

When hexachlorophene was fed to a cow, the intact material was
excreted via urine (0.24%) and feces (63.8%). No decomposition
was observed after incubation with rumen fluid and beef liver
10,000g supernate (St. John and Lisk, 1972).

Irradiation of hexachlorophene (I) in absolute ethanol and in
the absence of oxygen at > 260nm produced primarily the mono-
dechlorinated compounds II and III in almost equal amounts. Some
of the tetrachloro compounds IV and V were also detected. Irradia-
tion of product II gave IV and V; and irradiation of compound III
produced V and VI (Shaffer et al., 1970 and 1971).
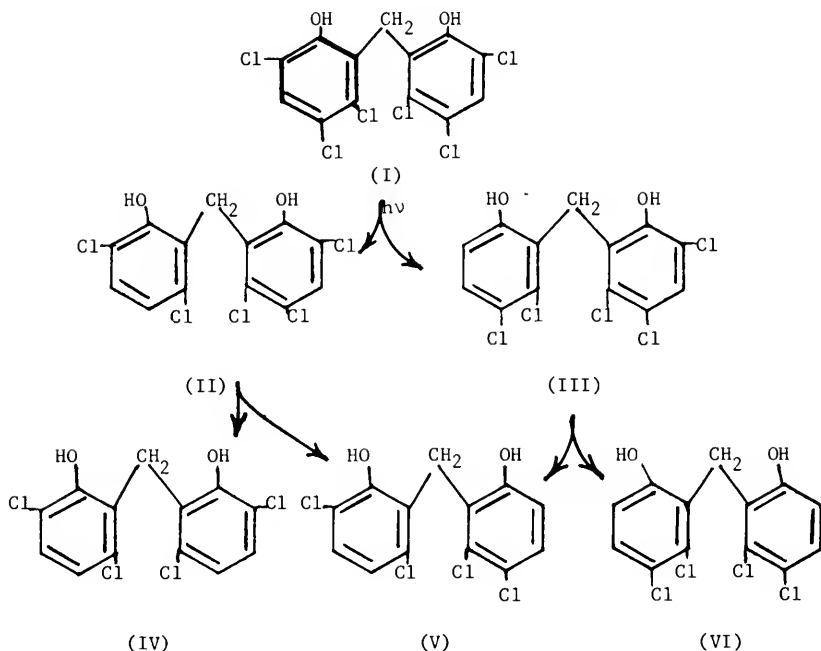
HINOSAN [O-Ethyl-S,S-diphenyl phosphorodithiolate]

Hinosan was incubated with mycelia of Pyricularia oryzae, the
causal fungus of rice blast. Analyses of the incubation mixture
indicated that the main metabolic pathway was the hydrolysis of
one P-S bond with subsequent hydrolysis of the other P-S bond
or ester linkage. Further hydrolysis yielded inorganic phosphate.
Some oxidation of the parent compound produced O-ethyl-S-hydroxy-
phenyl-S-phenyl phosphorodithiolate. Initial hydrolysis of the
ethyl ester linkage occurred also to yield small amounts of
S,S-diphenyl hydrogen phosphorodithiolate (Uesugi and Tomizawa,
1971).

After application of hinosan to rice plants, the main hydrolytic
products detected in the first four days were O-ethyl-S-phenyl
thiophosphate and S,S-diphenyl dithiophosphate. Subsequently,
O-ethyl phosphate and inorganic phosphate were observed. When
^{35}S-hinosan was used, S,S-diphenyl disulfide was detected in the
toluene extractables. S-Phenyl phosphate and benzene sulfonate
were detected in the water-extractable part. Sulfate was detected
as the final metabolite in the rice plant (Umeda, 1972).

Hinosan hydrolysis in rat, cockroach and E. coli proceeded mainly
by P-S cleavage as in P. oryzae. UV irradiation at 360mμ also
produced the same ester. Subsequent further cleavage produced ethyl-
dihydrogen phosphate (Uesugi et al., 1971).

At pH 7 and 27°C, 48% of the hinosan was hydrolyzed in 48 hours. The
half-life was 60 hours and k(min^{-1}) was calculated to be 2 x 10^{-4} (Uesugi
et al., 1971).

Hinosan
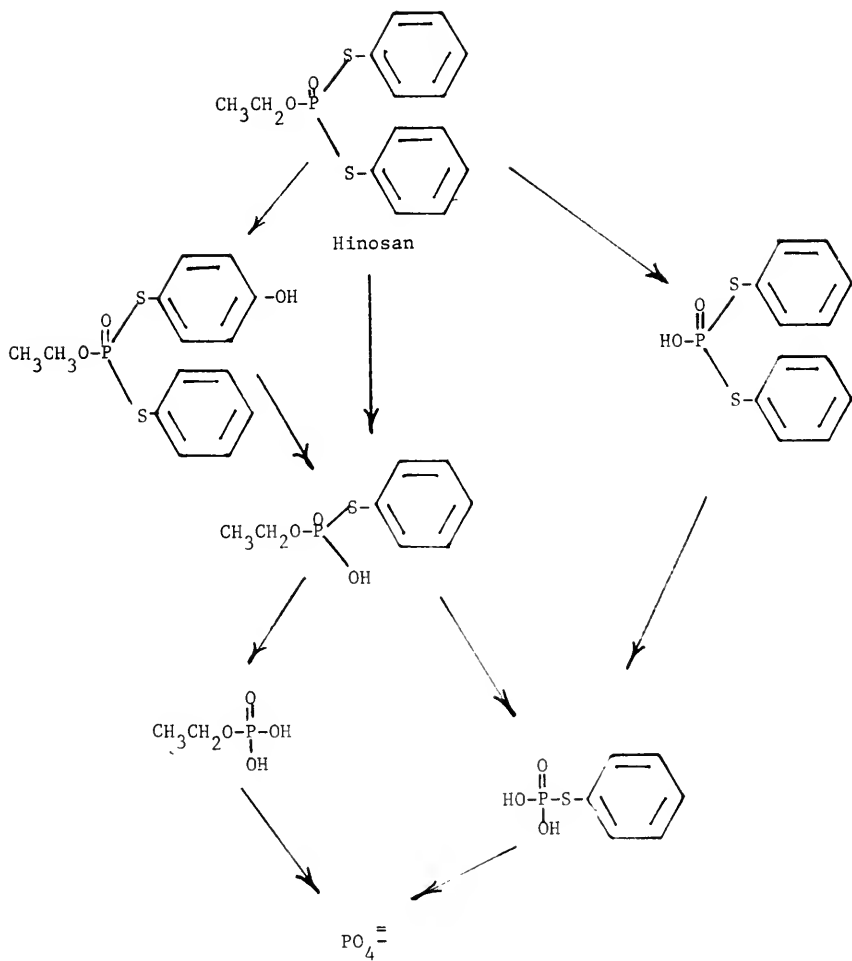
INEZIN [S-Benzyl O-ethyl phenylphosphonothiolate]

Mycelial cells of the rice blast fungus Pyricularia oryzae
metabolized inezin to ethyl hydrogen phenylphosphonothiolate or
ethyl hydrogen phenylphosphonate. The latter was hydrolyzed to
phenylphosphonate. This is probably further metabolized and
does not accumulate. Hydrolysis of inezin also produced small
amounts of toluene-α-thiol and benzyl alcohol. The latter was
oxidized to benzoic acid. The thiol was oxidized to dibenzyl
disulfide and/or benzylsulfonate which was also oxidized to
benzoic acid. Some hydroxylation of the benzyl moiety gave rise
to S-(m-hydroxybenzyl)-O-ethyl phenylphosphonothiolate which was
metabolized to unidentified water soluble metabolites (Uesugi
and Tomizawa, 1972).

Most of the inezin applied to plants was recovered unchanged.
In methanol extracts of treated rice plants, metabolites were
identified as O-ethyl phenyl phosphonothioate, desethyl inezin
and phenyl phosphonothioate (Endo et al., 1970).
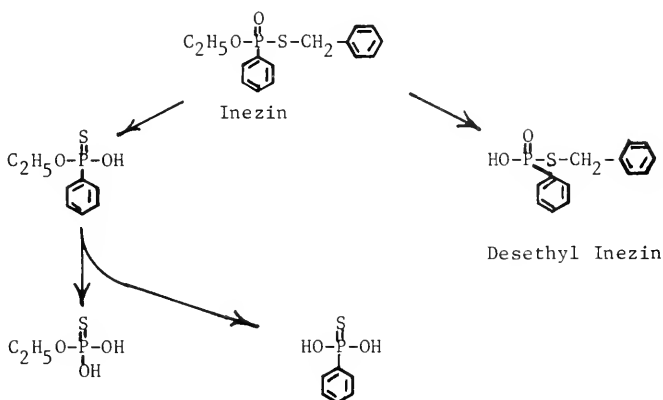
Cleavage of S-C bond in Inezin occured in rice plants and P. oryzae
and with UV light (Uesugi et al., 1971).

IODOFENPHOS [O,O-Dimethyl-O-(2,5-dichloro-4-iodophenyl) phosphate]

Over 80% of the iodofenphos administered to a rat was eliminated
in 24 hours in the urine. In addition to 5 unidentified metabolites,
iodofenoxon, desmethyl iodofenoxon, mono- and di-methyl phosphoric
acid, phosphoric acid, and dimethyl phosphorothioic acid were found
in the urine (Johannsen and Knowles, 1970).

After injection of iodofenphos into tomato plants, some of the
oxygen analog was detected in the leaves but not in the stems.
No other compounds were identified (Johannsen and Knowles, 1970).

KARSIL [N-(3,4-Dichlorophenyl)-2-methylpentanamide]

Fifteen different bacteria and fungi were isolated. Of these only
two pencillium species (one thought to be P. piscarium) and
another tentatively identified as Pullularia sp. gave positive
aniline tests when grown on Karsil agar plates. None of these
fungi formed TCAB. One of the two penicillium species also further
metabolized 2-methyl-valeric acid. The acylamidase in these
studies was an inducible enzyme and exhibited varying degrees
of activity against 25 acylanilides. In order of increasing
activity:

	Nanamoles arylamine released per µ mole substrate per 3 hrs.
N-(3,4-Cl$_2$-phenyl)-2-ethylbutyramide	0
N-(3,4-Cl$_2$-phenyl)-2,2-dimethylpropionamide	0
N-(2,5-Cl$_2$-phenyl)-2-methylpentanamide	0
N-(3,4-Dimethylphenyl)-2-methylpentamide	0
N-(3,4-Dimethylphenyl) propionamide	0
N'-(3,4-Cl$_2$-phenyl)-N,N-dimethylurea	0
Isopropyl-N-(3-chlorophenyl)carbamate	0
N-Phenylacetamide	4
N-(3,4-Cl$_2$-phenyl)-3,3-dimethylbutyramide	7
N-(2,4,5-Cl$_3$-phenyl)-2-methylpentamide	11
N-(3,4-Cl$_2$-phenyl) methacrylamide	40
N-(3,4-Cl$_2$-phenyl)-2-methylbutyramide	48
N-(3-Cl-4-methylphenyl)-2-methylpentanamide	55
N-(3,4-Cl$_2$-phenyl)-2-methylpentanamide (Karsil)	70
N-(4-Cl-phenyl)-2-methylpentanamide	106
N-(3-Cl-phenyl)-2-methylpentanamide	117
N-(3,4-Cl$_2$-phenyl)-4-methylpentanamide	144
N-(4-Br-phenyl) propionamide	188
N-(3,4-Cl$_2$-phenyl) acetamide	218
N-Phenylpropionamide	262
N-(3,4-Cl$_2$-phenyl)-2-chloropropionamide	340
N-(3-Cl-4-methylphenyl) propionamide	430
N-(3,4-Cl$_2$-phenyl) propionamide	520
N-(3,4-Cl$_2$-phenyl)-2-hydroxypentanamide	835
N-Phenylbutyramide	1000

(Sharabi and Bordeleau, 1969).

After cultivation of the fungus Rhizopus japonicus in the presence of
Karsil, a metabolite was isolated and identified by mass and n.m.r.
spectra as N-(3,4-dichlorophenyl)-3-hydroxy-2-methylpentamide
(Wallnofer et al., 1972).

<u>KELEVAN</u> (GC-9160) [Decachlorooctahydro-2-hydroxy-1,3,4-metheno-
2H-cyclobuta—(c,d)—pentalen-2-levulinic acid ethyl ester]

Kelevan was irradiated by UV in acetone and methanol. The mono-II
and di-II dechlorinated analogs were isolated and identified
(Parlar et al., 1972).
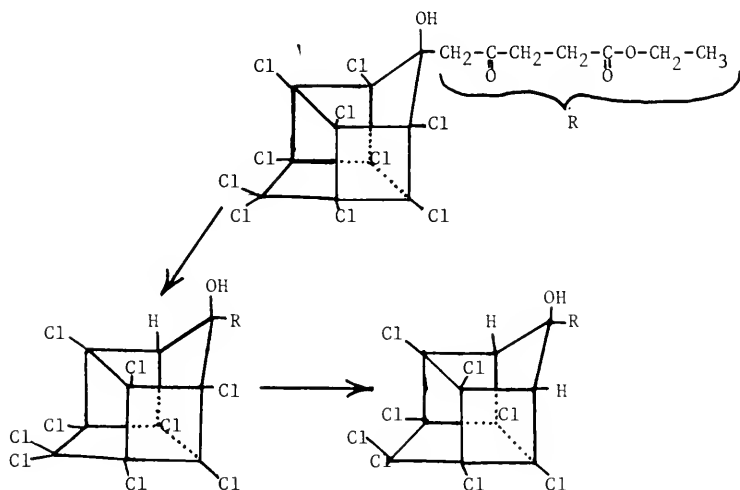
After oral ingestion of kerb by a cow, four metabolites were
found in the urine and identified by chromatography as compounds
VII, VIII, and XII. In a similar study with rats, compounds
III, IV, VI, VII, VIII and XI were found in both urine and feces;
compounds I, II and V, in feces only; and compounds XII, XIII and
XIV, in urine only (Yih and Swithenbank, 1971a and 1971c).

After foliar application of kerb to alfalfa, compounds I to X were
observed. However, the possibility was not eliminated that com-
pounds found in alfalfa were actually formed in the soil. Com-
pounds I to IX were observed in soil treated with the herbicide
(Yih and Swithenbank, 1971a and 1971b; Yih et al., 1970).
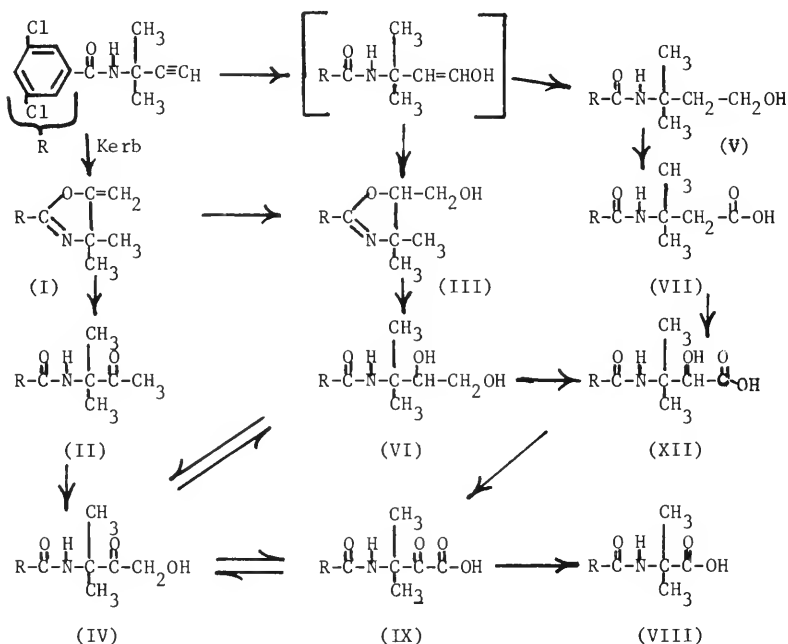
KITAZIN P [S-Benzyl O,O-diisopropyl phosphorothiolate]

Labeled kitazin P was incubated with mycelia of the rice blast
fungus Pyricularia oryzae. The fungicide was taken up from the
medium by the mycelia and metabolized primarily to water-soluble
products which were released into the medium. The main metabolite
was identified as O,O-diisopropyl hydrogen phosphorothiolate.
From co-chromatography with known materials, several other metabo-
lites were identified as inorganic phosphate, diisopropyl phos-
phate and mono-isopropyl phosphate. Another compound is believed
to be S-benzyl-O-isopropyl hydrogen phosphorothiolate. Hydroxyla-
tion also gave rise to some S-(m-hydroxybenzyl)-O,O-diisopropyl
phosphorothiolate (Tomizawa and Uesugi, 1972).

In rats, cockroach and rice plant, S-C cleavage of kitazin P lead to
O,O-diisopropyl hydrogen phosphorothiolate (Uesugi et al., 1971).
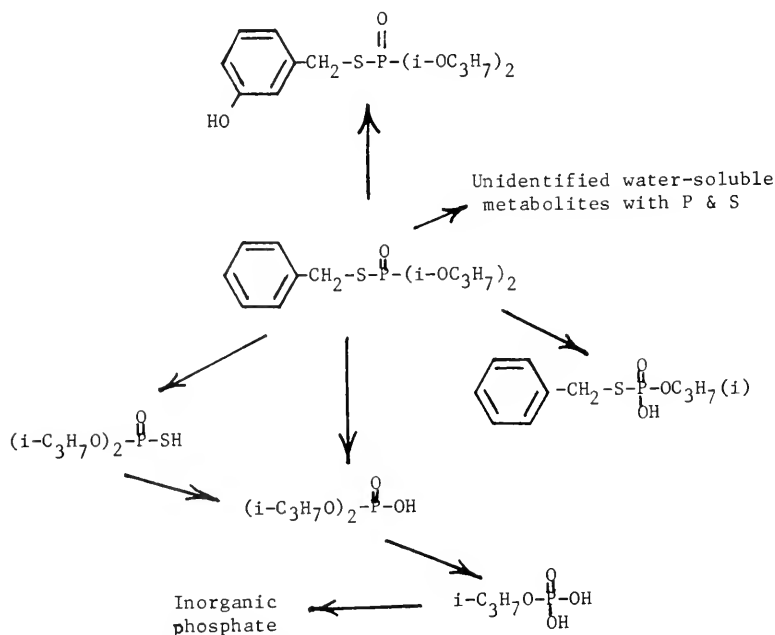
At pH 7 and $27^{\circ}C$, 1.6% of kitazin P was hydrolyzed in 48 hours. The half-
life was 80 days and $k(min^{-1})$ was calculated to be 6×10^{-6} (Uesugi et al.,
1971).

<u>LANDRIN</u> [<u>N</u>-Methyl-2,3,5-(and 3,4,5)-trimethylphenyl carbamate]

The metabolism of 3,4,5- and 2,3,5-trimethylphenyl methylcarbamates
was investigated with living bean plants, mice, houseflies, and
mixed-function oxidase systems prepared from mouse liver or house-
fly abdomens. The major point of attack involves oxidation of the
ring methyl groups. In the bean plants, houseflies and mice,
rapid conjugation of the hydroxymethyl compounds occurred. Some
hydrolysis and <u>N</u>-methyl oxidation also occurred. When landrin was
applied to bean leaves and exposed to sunlight, both trimethyl
isomers decomposed rapidly to form the 4-hydroxymethyl and <u>N</u>-
hydroxymethyl derivatives from the 3,4,5-isomer and the 3-hydroxy-
methyl, 5-hydroxymethyl, and <u>N</u>-hydroxymethyl derivatives from the
2,3,5-isomer. Several other materials, believed to be products
of oxidation of two or more methyl groups, were observed but not
identified (Slade and Casida, 1970).

1=Snapbean plants; 2=Houseflies; 3=Mice; 4=Photodecomposition on foliage;
5=Mouse liver/ housefly abdomen
enzyme systems

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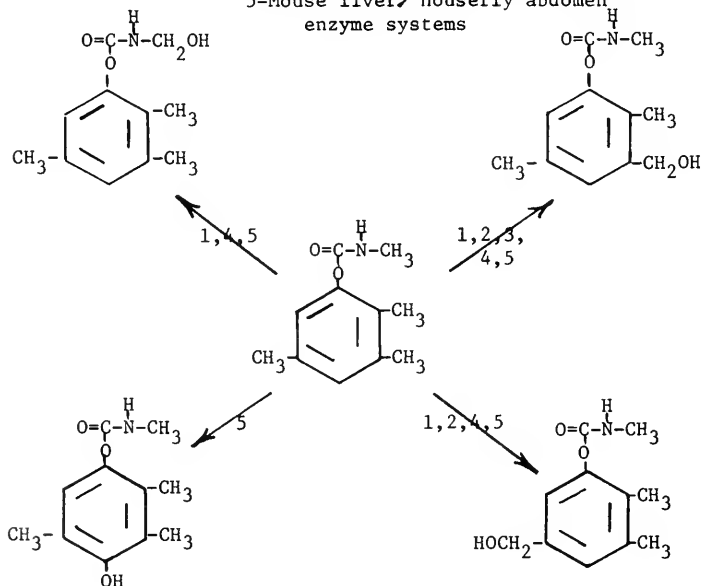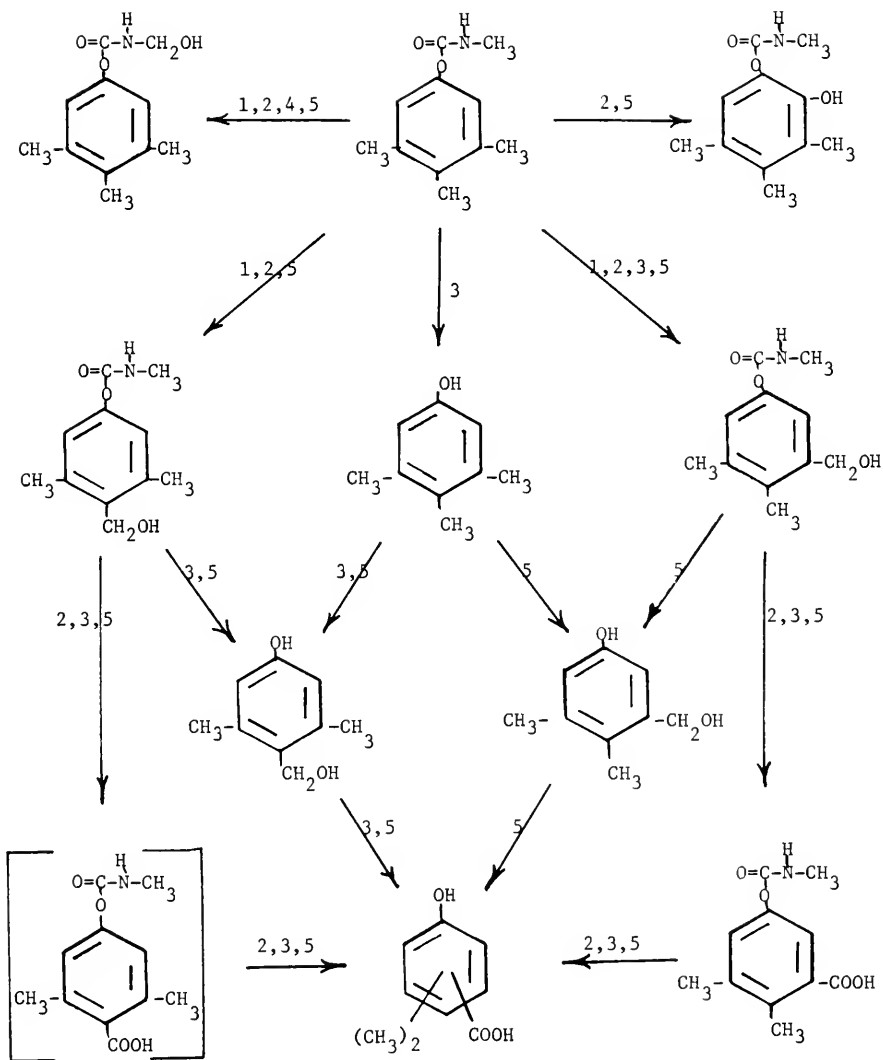
1=Snapbean plants; 2=Housefly; 3=Mice; 4=Photodecomposition on bean
foliage; 5=Mouse liver microsome and housefly abdomen enzyme systems

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TETRAETHYLLEAD (TEL)

Tetraethyl lead (TEL) was rapidly converted after intravenous administration to rats to triethyl lead. Within 24 hours after administration of TEL, 50% of total lead in soft organs was triethyl lead and highest levels were in liver, blood, kidney and brain. In rat and man, TEL was converted to triethyllead wheras in rabbits dealkylation proceeded to inorganic lead. Toxic symptoms arising in vivo following TEL administration result from the formation of triethyllead. In vitro studies showed that rat and rabbit liver microsomes, as well as homogenates of kidney and brain, could also dealkylate TEL to triethyllead (Bolanowska, 1967 & 1968; Bolanowska and Garczynski, 1968; Bolanowska and Wisniewska-Knypl, 1971).

After injection into rats, TEL breaks down to triethyl lead (TREL) which is responsible for the toxic effects. TREL is stable and inhibits lactate utilization and glucose oxidation by brain brei and slices. Diethyl lead (DEL) is much less toxic and effects are different. DEL reacts with B.A.L. but not with E.D.T.A.; tetra- and tri-ethyl lead do not react with either complexing agent (Cremer, 1959).

<u>LG-63</u> [<u>O</u>-Ethyl-<u>S</u>-hexyl methylthiophosphonate]

Decomposition of LG-63 was very slow in blood, liver, kidney and brain tissues of albino rats(Rozengart et al., 1971).

MALATHION [0,0-dimethyl-S-(1,2-di(carbethoxy)ethyl phosphorodithioate]

The biochemistry of malathion was studied in resistant and susceptible strains of adult bedbugs. Decreased penetration in resistant strains probably augmented other resistance mechanisms. Total hydrolysis of malathion was greater with homogenates of the resistant insect than with that of the susceptible bugs. Malathion and malaoxon were present in higher proportions in homogenates of the susceptible strain. The hydrolytic products (malathion mono- and di-acids, demethyl malathion, and diethyl mercaptosuccinate) were present in greater quantities in the homogenate of the resistant strain. Diethyl malate, malic acid, mercaptosuccinic acid, and some unknowns were also observed (Feroz, 1971).

Resistant Triboluim castaneum degraded malathion more rapidly than the susceptible strain and produced carboxyesterase products more rapidly. Malaoxon rose higher in the susceptible beetles. Phosphatase products were produced at about the same rate in both strains (Dyke and Rowlands, 1968).

In vitro studies with mouse liver homogenates indicated that only about half of the total malaoxon detoxification was accounted for by carboxyesterase hydrolysis. The studies suggested that malathion was also inactiviated by bending to noncritical binding sites of carboxyesterase (Cohen and Murphy, 1972).

Degradation of malathion in soil was rapid and was related to the degree of adsorption, suggesting a chemical mechanism. In soil-free acid systems (>pH 2) hydrolysis did not occur, was slow at pH 9 (<50% in 20 days), and rapid at pH 11 (>99% in 1 day). At pH 9 hydrolysis produced thiomalic acid, dimethyl thiophosphate, and diethyl thiomalate. In soil both esters were hydrolyzed, but not at the same rate, and diethyl thiomalate accumulated in some soils (Konrad et al., 1969). Studies have shown that the rate of malathion hydrolysis increased rapidly above a critical moisture level. At temperatures of $70^{\circ}F$ and $90^{\circ}F$, the critical moisture level was found to be 11.6% and 11.8%, respectively (Minett et al., 1968).

A homolog of malathion, found as a residue on malathion field-sprayed kale, was characterized as containing a butyl ester moiety in place of one ethyl group (Gardner et al., 1969).

Bean plants grown in nutrient solution treated with malathion absorbed small amounts of malathion and converted it to the P=O analog (El-Refai and Hopkins, 1972).

During midgut penetration by malathion in Blaberus discoidalis, malaoxon and the monocarboxylic acid were found in the chloroform extract. In the water extract, diethylmalate and the dicarboxylic acid were observed. The same pattern was found with Mus musculus and Manduca sexta (Shah and Guthrie, 1970).

Malathion was incubated with Aspergillus niger, Penicillium notatum and Rhizoctonia solani. Highest activity was observed with Penicillium notatum which metabolized 76% of the applied malathion. Rhizoctonia solani was inhibited above 2 mg/100ml. Differences between the Penicillum sp. and Aspergillus sp. was only quantitative. Metabolites observed included: thiophosphate, monomethyl phosphate, malathion diacid, malathion monoacid, dimethyl phosphate, dimethyl phosphorothioate, and demethyl phosphorodithioate.

Malathion was incubated with Rhizobium leguminosarum and R. trifolii. Analyses of the media indicated that these microorganisms lacked oxidative necessary systems for production of malaoxon. In the case of R. leguminosarum, malaoxon was completely absent; and with R. trifolii, only negligible amounts. The metabolic processes were essentially hydrolytic. In addition to inorganic phosphates and/or thiophosphates, malathion mono- and di-acids, dimethyl phosphate, $\underline{O},\underline{O}$-dimethylphosphorothioate, and $\underline{O},\underline{O}$-dimethylphosphorodithioate were observed (Mostafa et al., 1972).

The reaction of peroxytrifluoroacetic acid with malathion produced dimethyl phosphorothioic acid. Some unidentified material was also present (Ptashne and Neal, 1972).

MALEIC HYDRAZIDE (MH)

When maleic hydrazide (MH) was applied to corn and pea seedlings,
the MH was bound to some material in the roots. The complex is
stable for about one week but treatment with aminoethanol releases
the MH. Binding is blocked by azide and dinitrophenol; but inhibitors
of protein and DNA synthesis do not inhibit binding (Nooden, 1970).

MEOBAL [N-Methyl-3,4-xylylcarbamate]

Meobal (I) was orally administered to male Wistar rats. Collected
urine contained only traces of unchanged Meobal. The most abundant
metabolite was 3-methyl-4-carboxyphenyl-N-methylcarbamate (V).
Other oxidation products identified were 3-hydroxymethyl-4-
methylphenyl-N-methylcarbamate (II) and its glucuronide (III),
3-(or 4)-hydroxymethyl-4(or 3) methylphenol glucuronide (IV),
3-methyl-4-carboxyphenol (VI) and its glucuronide (VII), 3-
methyl-4-carboxyphenyl-N-hydroxymethylcarbamate (VIII). Hydrolysis
products included 3,4-dimethylphenol (IX) and its sulfate (X) and
glucuronide (XI) conjugates. Additional metabolites were present
but not identified (Miyamoto and Fukunaga, 1971; Miyamoto et al.,
1969).

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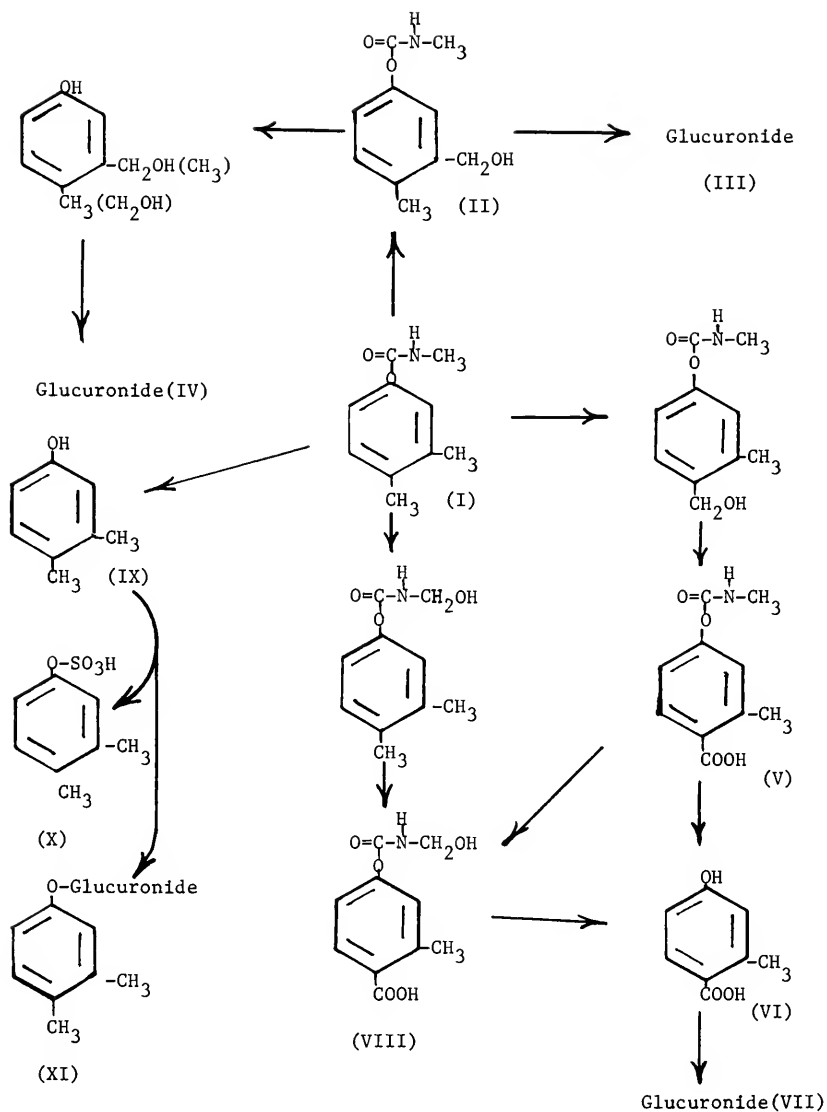
MERCURY

INORGANIC MERCURIALS

Mercuric Chloride (MC)
Mercuric Nitrate
Mercuric Sulfide

Several strains of Escherichia coli were found that were resistant
to $HgCl_2$, though sensitive to Ni, Co, Cd and Zn ions. The system
vaporized a ^{203}Hg compound, probably metallic mercury, from $^{203}HgCl_2$.
NADPH was essential for the vaporization (Komura and Izaki, 1971;
Komura et al., 1971). From a cell-free extract of mercury-
resistant Pseudomonas, an enzyme was obtained which catalyzed the
reduction of mercury in organic as well as inorganic mercurials
to metallic mercury. A prosthetic group of the enzyme was identified
as FAD. Mercuric ions of MC were reduced to metallic mercury
(Furukawa and Tonomura, 1972; Tonomura et al., 1968).

After oral administration of $^{203}HgCl_2$ to a cow, analyses showed that
peak concentrations in the metabolic products of the cow were
reached between 24-48 hours. After 48 hours, fecal levels dropped
but milk, urine, plasma and erythrocyte levels remained relatively
constant. The biological half-life of $^{203}HgCl_2$ in the cow was
28.5 hours (Potter et al., 1972). In rats, mercuric chloride
stimulated biosynthesis of metallothionein (Wisniewska et al., 1972).

Mercuric sulfide was incubated with aquarium sediment. Results of
these studies showed that even in this form mercury was available
for biological methylation, although at a considerably lower rate
than when mercury is present as Hg^{++} (Fagerstrom and Jernelov, 1971).

Guppies (Poecilia reticulata) were placed in a tank containing a
sediment to which mercuric chloride or mercuric sulfide had been
added. Analyses indicated a rapid increase in the levels of mercury
found in the fish. Passive transfer by solution was eliminated
by extraction of sediment samples with 0.3 $N-HNO_3$. This resulted
in solubilizing 1% of the contained mercury. Presumably mercury,
slowly released to the water by microbial activity in the sediment,
was absorbed by the fish. Added mercurials were proportionately
much less rapidly mobilized than was the preexisting mercury
(Gillespie and Scott, 1971).

[203]Hg-Mercuric nitrate was administered intravenously and intra-muscularly to rats. Distribution to all organs was rapid following intravenous injection. Fecal excretion, rapidly cleared initial accumulation in the liver. Mercury content of the kidney increased until it accounted for about 85 to 90% of the total body burden. The study indicated three phases in the clearance of mercury from the rats. A rapid phase involved 35% of the dose, lasting for a few days; a slower phase involved 50% of the dose with a half-time of 30 days; and a slow phase involving 15% of the dose with a half-time of about 100 days (Rothstein and Hayes, 1960).

Early studies indicated that microorganisms could methylate mercury and that dimethyl mercury formed (Jensen and Jernelov, 1967 and 1968). In other studies, a methanogenic bacterium Methanobacterium omelianskii, as well as solutions of methylcobalamine, were capable of methylating mercury. Dimethyl mercury was the initial reaction product (Wood et al., 1968; Imura et al., 1971). Subsequently, the methylation of inorganic mercury was demonstrated after incubation with rotten fish (Xiphophorus maculatus) as well as bottom sediments (Jensen and Jernelov, 1969).

Studies were undertaken with Neurospora crassa in whose metabolism Vitamin B_{12} is not known to be involved. The results with Hg^{++} tolerant isolates indicated higher methylating efficiency than with other strains and suggested methylation of mercury as a detoxification process in Neurospora. In this organism, methylation apparently involved S-adenosyl methionine as the methyl donor (Landner, 1971). In addition to the methane and methionine syn-thetases, acetate synthetase has also been implicated in mercury methylation (Wood, 1971).

Mucus scraped from pike also methylated divalent mercury (Jernelov, 1968). When mercuric chloride or PMA was incubated with sewage sludge, vaporization of mercury from the culture was observed (Yamada et al., 1969).
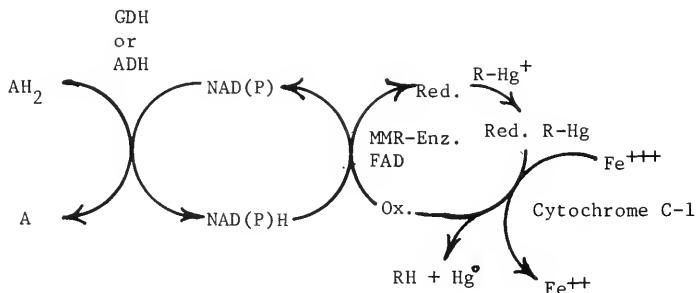
The mobilization of mercury from sediments to guppies was also
studied. Aerobic and anaerobic sediments, to which various mercury
compounds were added, were placed in aquaria. Guppies (Poecilia
reticulata) were then placed in the aquaria. Periodically analyses
of fish were conducted to determine total mercury content and
the proportion of methylmercury present. Under aerobic conditions,
little mercury appeared in the fish when mercuric chloride or
sulfide were used; but total mercury concentrations rose rapidly
in fish exposed to sediments containing mercury metal. The
maximum proportion of methylmercury in the fish was 30% for metallic
mercury, 40% for mercuric chloride, and 45% for mercuric sulfide.
Under anaerobic conditions, mobilization was low and methylation
was significant (40% of total mercury in fish) only for mercuric
chloride. Greater mobilization and methylation occurred in low
mercury-containing sediment from sites of industrial pollution than
in sediments containing higher mercury content. It was also observed
that lignosulfate stimulated mercury methylation under anaerobic
conditions but not aerobically (Gillespie, 1971).

In aqueous solutions, in the presence of methylcobalamin and mercuric
chloride, hydroxycobalamin and methylmercury cation were formed
(Bertilsson and Neujahr, 1971).

Inorganic mercury salts were also methylated in aqueous solution by
trimethylsilyl salts, commonly used as n.m.r. reference compounds
(DeSimone, 1972).

Studies indicated that livers of yellowfin tuna and albacore have high
activity in formation of methylmercury from $HgCl_2$. This activity was
not found in the meat. When the liver-$HgCl_2$ mixtures were exposed to
visible light during incubation, formation of methyl mercury was
reduced by about 75%. This indicated possible participation of methyl-
cobalamin in the methylation (Imura et al., 1972).

Methyl mercury acetate = MMA
Methyl mercury chloride = MMC
Methyl mercury dicyanodiamide = MMD
Methyl mercury hydroxide
Methyl mercury nitrate
2-Methoxyethyl mercury chloride = MEMC
Ethyl mercury chloride = EMC
Ethyl mercury phosphate = EMP
Butyl mercury chloride = BMC
Phenyl mercury acetate = PMA
Phenyl mercury chloride = PMC
Phenyl mercury propionate = PMP

All organo-mercurials tested apparently release inorganic mercury
in animal tissues; but the different mercurials release divalent
mercury at widely varying rates after administration to animals
(Clarkson, 1969).

From a cell-free extract of mercury resistant Pseudonomas, an
enzyme was obtained which catalyzed the reduction of mercury in
organic and inorganic mercurials to metallic mercury. A prosthetic
group of the enzyme was identified as FAD. When this enzyme was
incubated with MMC, metallic mercury and methane were produced.
PMA gave rise to metallic mercury and benzene; EMP, metallic
mercury and ethane (Furukawa and Tonomura, 1972; Tonomura et al.,
1968).

In rats, only methyl-, ethyl-, and n-propyl- mercury derivatives
exhibited neurotoxicity. The n-butylmercury compounds did not.
Some quantitative differences in distribution were observed between
ethyl- and n-butyl- mercury compounds. After administration of
n-butylmercuric chloride (BMC), more mercury was found in blood
than in muscle and more mercury was excreted via feces as compared
to EMC. Relatively high levels of mercury in the brain were
observed for EMC and BMC and removal was slower than from all other
organs. The ratio of mercury concentration in the brain to that in
the plasma was larger for alkylmercury than for inorganic or phenyl-
mercury compounds; the ratio for EMC (2 to 3) was larger than for
BMC (ca 1). This difference seemed to be correlated with the
specific neurotoxicity of short carbon chain alkylmercurials. No
distinct difference was noted in distribution or excretion of
mercury between EMC and ethylmercury cysteine (EMCy) exposure.

It was noted too that phenylmercury compounds rapidly decompose
to inorganic mercury derivatives in the body; that, early after
administration, distribution patterns of PMC in organs and blood
are more similar to those of alkylmercurials than to those of MC;
and that in the later period after administration, the distribution
patterns become similar to that of MC (Gage, 1964; Miller et al.,
1960; Sebe and Itsuno, 1962; Suzuki et al., 1963 & 1964; Takeda
et al., 1968; Ulfvarson, 1962).

Organomercurials decomposed when placed in tissue culture solutions.
The mechanism was not understood. Decomposition rates were in the
order EMC>BMC>PMC>MMC. PMA decomposed when combined with wheat roots
within 24 hours. When roots were cultured for one week, PMA decomposed
with very small and almost constant rate (Takeda and Isobe, 1971).

Albino rats of both sexes were administered mercurials via the drinking
water. When the compound in question was administered continuously
with a constant dosage δ per unit time, the excretion approached the
differential equation $dx = \cdot dt(\delta - \alpha x)$ where x=concentration of
compound in body
α=excretion proportionality
constant

Resorption process approached:

$$x = \frac{\delta}{\alpha}(1-e^{-\alpha t})$$

If $\alpha x = y =$ amount excreted per unit time and body weight, then

$$y = \delta(1-e^{-\alpha t})$$

The half-life expressed in terms of the excretion constant was

$$T_{1/2} = \frac{e \log 2}{\alpha} = \frac{0.69}{\alpha}$$

The biological half-life of methyl mercury salts was found to be between
15 and 20 days; methoxyethyl mercury hydroxide, 4 to 10 days; mercury
(II) nitrate and phenylmercury hydroxide, between 4 and 10 days (Ulfvarson,
1962).

Methyl mercury acetate

MMA was administered intramuscularly to piglets. The stomach was the
site of maximal absorption of the mercury from the alimentary tract.
Unchanged methyl mercury was found in all tissues; but in the kidneys
and liver only it was found in an altered form. Excretion of mercury,
mostly in a changed form, was excreted slowly from the body (Platonow,
1968).

Soybean sprouts absorbed MMA through the roots. A portion of the MMA
was decomposed to inorganic mercury in the plant. In young wheat
plants, inorganic mercury was found in all parts of the plant after
absorption (Takeda et al., 1971).

Methyl mercury chloride

Methyl mercury chloride (MMC) was injected intravenously into female
rats. Inorganic mercury accounted for the highest proportion of
total mercury in the excretory organs and in feces. Release of
inorganic mercury was the major biotransformation pathway for methyl
mercury in rats (Norseth and Clarkson, 1970a). The site of this bio-
transformation is probably not restricted to the liver. Other studies
have indicated that methyl mercury chloride releases inorganic mercury
when allowed to stand in buffered solutions of cysteine at physiological
pH. Thus, the transformation reaction may not be catalyzed by an
enzyme but may result from a chemical reaction of the organomercurial
with thiol groups (Norseth and Clarkson, 1970b).

After injection of methyl mercuric chloride into mice, inorganic
mercury was found in blood, brain, liver, kidney, spleen, intestinal
cells, bile, and feces. Excretion of inorganic mercury was primarily
via feces (Norseth, 1971).

A strain of Pseudomonas, isolated from soil, was found to be resistant
to organic and inorganic mercurials. The organism absorbed large
amounts of mercury on the cell surface from culture media containing
mercurials. Vaporization of the adsorbed mercury was induced. In
addition to metallic mercury, methane was produced when MMC was
aerobically incubated with the organism (Furukawa et al., 1969). A
cell-free extract of this organism gave similar results. The studies
indicated that a sulfhydryl compound and NADH were required (Tonomura
and Kanzaki, 1969a and 1969b).

Three groups of pregnant Charles River rats were given oral doses of methyl mercury chloride. Transfer of methyl mercury to the young occurred but it was not determined that this was via the placenta or the mother's milk after birth. Clearance rates of methyl mercury were more rapid in the young than in the dams in both the blood components and brain (Casterline and Williams, 1972).

Biotransformation, whose mechanism is not known, occurred in the intestinal tract of rats. The substrates were probably methyl mercuric protein complexes (Norseth and Clarkson, 1971; Clarkson et al., 1971). Germ free rats were given a subcutaneous injection of Hg as methyl mercuric chloride. Analyses indicated that the release of inorganic mercury in the gastrointestinal tract in rats was not caused by microorganisms (Norseth, 1971).

Methyl mercury dicyanodiamide

After repeated subcutaneous dosage of rats with methyl mercury dicyanodiamide, there was no clear indication of a steady state being reached after six weeks. Organic mercury accumulated in all tissues. Breakdown of MMD to inorganic mercury was low (Gage, 1964).

Methyl mercury hydroxide

^{14}C-methyl mercury hydroxide was administered to mice. Analyses indicated that initially a small amount of the material was degraded to $^{14}CO_2$ and inorganic mercury. Most of the material administered was stored in tissues as mercury (Norseth, 1971).

Methyl mercury nitrate

After oral intake of labeled methyl mercuric nitrate by three male volunteers, ^{203}Hg accumulated in the liver and head. The main excretory route was the feces but urinary excretion increased up to 30 days after intake. The biological half-life was found to be 70 to 74 days. Decline of ^{203}Hg in the head was not as rapid as in the rest of the body (Aberg et al., 1969).

Dimethyl mercury

^{203}Hg-Dimethyl mercury was injected into mice. Elimination by exhalation was obvious as early as 1 hour and still more so after 16 hours. Dimethyl mercury behaved as a chemically inert substance towards tissues and, in accordance with its lipophilic nature,

accumulated only in fat tissue and in tissues containing lipids or lipophilic cells. Activity in other tissues corresponded to a non-volatile metabolite identified as methyl mercury (Ostlund, 1969).

2-Methoxyethylmercury chloride

When ^{14}C-MEMC was administered subcutaneously to rats, 6% of the label appeared as CO_2 within 48 hours in the expired air. Pyrolysis of the air provided an additional 45%. The radioactive component has been identified as ethylene. Within 5 days of dosing, about one-quarter of the dose appeared in the urine as total mercury. A small portion of the dose was excreted unchanged in urine and a large amount in bile with some resorption from the gut. The half-time for breakdown was about 1 day (Daniel and Gage, 1968; Daniel et al., 1971).

Ethylmercuric Chloride

^{203}Hg-Ethylmercuric chloride (EMC) was administered to rats. Analyses showed that EMC was bound to hemoglobin and, after pronase digestion, was detected as S-EMC cysteine. A part of the administered dose was also metabolized to inorganic mercury which accumulated to a higher level in kidney than in liver. In the organs, organic mercury was bound to protein (Takeda, 1968 and 1970).

After intramuscular and oral administration of ethylmercury chloride to chicks and rats, the EMC was absorbed unchanged. Metabolism of EMC was slow and intact EMC was detectable in the liver and kidneys for 21 days (Miller et al., 1961).

Ethylmercuric Phosphate

A strain of pseudomonas, isolated from soil, was found to be resistant to organic and inorganic mercurials. The organism adsorbed large amounts of mercury on the cell surface from culture media containing mercurials. Vaporization of the adsorbed mercury was induced. In addition to metallic mercury, ethane was produced when EMP was aerobically incubated with the organism (Furukawa et al., 1969). A cell-free extract of this organism gave similar results. The studies indicated that a sulfhydryl compound and NADH were required (Tonomura and Kanzaki, 1969a and 1969b).

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Phenyl mercury acetate

PMA was absorbed unchanged into the circulation after subcutaneous
administration to rats or after intramuscular or per os
administration to chicks, rats and dogs. It was easily removed by
the liver and kidneys where it was rapidly metabolized and excreted
via the feces and urine as inorganic mercury. A steady state was
reached by the end of two weeks (Gage, 1964; Miller et al., 1960).

PMA-^{203}Hg was administered to rats by intravenous injection.
The kidneys were removed, converted to a powder, and hydrolyzed
with pronase. It was shown that some of the PMA had been converted
to inorganic mercury. Some of the label could not be solubilized
with pronase, indicating conjugation with components other than
protein (Kido et al., 1967).

Microorganisms converted PMA to diphenylmercury and another
unidentified metabolite. No methyl mercury derivatives were
observed (Matsumura et al., 1971).

A strain of pseudomonas, isolated from soil, was found to be
resistant to organic and inorganic mercurials. The organism
adsorbed large amounts of mercury on the cell surface from culture
media containing mercurials. Vaporization of the adsorbed mercury
was induced. In addition to metallic mercury, benzene was produced
when PMA was aerobically incubated with the organism (Furukawa et
al., 1969). A cell-free extract of this organism gave similar
results. The studies indicated that a sulfhydryl compound and
NADH were required (Tonomura and Kanzaki, 1969a and 1969b).

Biological half-life in Rats

	$T_{1/2}$ (days)
PMA	22.0
PMC	27.9
EMC	15.3 and 48.8
MC	7.3
MMC	8.5

(Kido et al., 1968)

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^{14}C-Labeled phenylmercury acetate was subcutaneously administered to rats. About 85% of the label appeared in urine within 4 days and 5% in the breath. Most of the mercury was excreted in feces, with about 12% in urine. Most of the label in urine was associated with sulfate and glucuronic acid conjugates of phenol. It was speculated that the phenylmercury was hydroxylated before cleavage of the carbon-mercury bond (Daniel and Gage, 1971). In other studies, the greater part of a single subcutaneous dose in rats was broken down in the tissues to yield inorganic mercury, which is excreted mainly in feces, and conjugates of phenol and quinol, which were excreted in urine. Studies with liver homogenates released inorganic mercury and benzene. No elemental mercury was formed (Daniel et al., 1972).

Soybean sprouts absorbed PMA through the roots. A portion of the PMA was decomposed to inorganic mercury in the plant. In young wheat plants, inorganic mercury was found in all parts of the plant after absorption (Takeda et al., 1971).

PMA decomposition was accelerated by cysteine, glutathione, and di-hydrothioctic acid. Reaction of glutathione with alkylmercuric compounds indicated that the decomposition mechanism was different than with aryls. Decomposition rates for the reaction of alkylmercurials with glutathione depended on the kind of alkyl group. Methyl, n-propyl and n-butyl derivatives exhibited similar decomposition curves. The ethylmercuric compound, however, exhibited irregular behavior (Isobe et al., 1971).

Diphenylmercury

Acidolysis of diphenylmercury in aqueous solution at 25°C and pH4 exhibited a half-life of eight days (Wolfe et al., 1972).

MESUROL (Methiocarb) [N-Methyl-4-methylthio-3,5-xylylcarbamate]

In vitro metabolies of mesurol was studied in liver, kidney and blood of dogs and rats. The rat preparations were more active than those of the dog. The major distribution of radiolabeled materials was the same for both species. However, differences were observed in minor pathways. The major ether-extractable metabolite was mesurol sulfoxide in both species. N-hydroxymethyl mesurol was also observed for the first time. Other metabolites were not identified (Wheeler and Strother, 1971).

When rat and human liver was incubated with mesurol, about a dozen metabolites were observed on TLC-radioautograms. The major metabolite was mesurol sulfoxide. Several metabolic products, which appeared on radioautograms from the human liver studies, were not observed in the rat studies. Hydrolysis yielded the phenolic moiety of mesurol (Strother, 1970 and 1972).

METHIDATHION [$\underline{S}$-(2-Methoxy-5-oxo-Δ^2-1,3,4-thiadiazolin-4-yl)methyl—
$\underline{O},\underline{O}$-dimethyl phosphorodithioate]

Methidathion degraded rapidly in soil. Fifty percent of the applica-
tion decomposed in less than 2 weeks and more than 90% disappeared
within 16 weeks. After 16 weeks, 40-66% of ring or methyl side
chain ^{14}C-label was expired as $^{14}CO_2$ (Getzin, 1970).

METHIOCHLOR [2,2-Bis(p-methylthiophenyl)-1,1,1-trichloroethane]

Methiochlor was metabolized in mice by oxidative processes to the
sulfoxides (III and IV) and sulfones (V and VI). In urine the major
metabolite was the bis(methylsulfinyl) analog (IV); in the feces,
the bis(methysulfonyl) analog (VI) (Kapoor et al., 1970).

In DDT-resistant houseflies, in addition to compounds III, IV, V
and VI, the ethylene analog (II) was also found. The salt marsh
caterpillar excreta contained over 90% unchanged methiochlor, less
than 1% as the ethylene analog and some monosulfoxide. The homogenate
contained a small amount of bis-sulfoxide in addition to methiochlor,
ethylene analog and monosulfoxide (Kapoor et al., 1970).

In a model ecosystem containing Sorghum halpense, Oedogonium
cardiacum, Daphnia magna, Physa snails, Culex quinquefasciatus
larvae and Gambusia affinis, methiochlor was metabolized to
compounds II, III, IV, V and VI and some unidentified polar
metabolites (Kapoor et al., 1970).

(II)

(I)

(III)

(IV)

(VI)

(V)

252
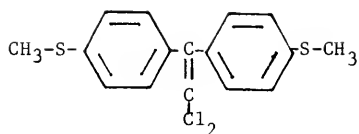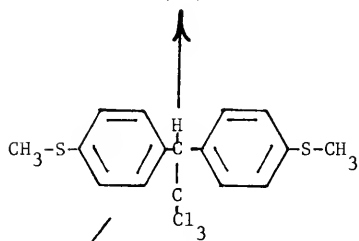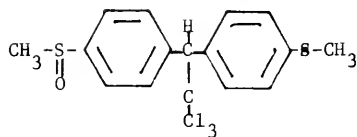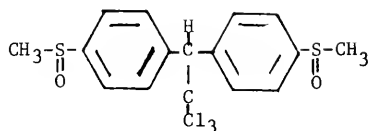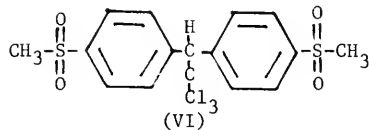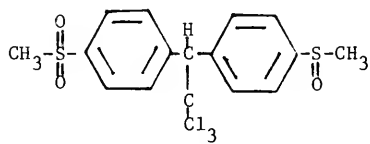
METHOMYL [S-Methyl-N-(methylcarbamoyloxy) thioacetimidate]

When young cabbage plants were treated foliarly with methomyl,
less than 3% of the material remained one week after treatment.
When S-methyl 1-^{14}C-N-(methylcarbamoyoxy)thioacetimidate was used,
over 20% of the label volatilized as $^{14}CO_2$ and 1-^{14}C-acetonitrile.
After total decomposition of the methomyl, the remainder of the
label was reincorporated in natural plant components. No S-oxide
or S,S-dioxide was detected. Labeled lipids, fatty acids, glycolic
acid, tartaric acid, sugars and other products have been detected
(Harvey, 1971).

<u>Methoxychlor</u> [1,1,1-Trichloro-2,2-bis(<u>p</u>-methoxyphenyl)ethane]

Urine and feces were collected from mice fed labeled methoxychlor.
Of the recovered radioactivity, 90% was in the feces and 10% in
urine. Some dehydrochlorination and O-dealkylation occurred to
give compounds II, III, IV, V and VI. <u>In vitro</u>, incubation of mouse
liver microsomes with methoxychlor gave compound II and a trace of
VII (Kapoor et al., 1970). The salt marsh caterpillar exhibited
only a low capacity for O-dealkylation, as compared to the mouse.
Excreta contained 96% methoxychlor and traces of compound VII and
conjugates. DDT-resistant house flies metabolized methoxychlor to
compound III and conjugates (Kapoor et al., 1970).

In a model ecosystem containing <u>Sorghum halpense</u>, <u>Oedogoium</u>
<u>cardiacum</u>, <u>Daphnia magna</u>, and <u>Physa</u> snails, methoxychlor was converted
to compounds II, III, VIII and some unidentified compounds (Kapoor
et al., 1970).

Metabolism of methoxychlor was qualitatively the same in susceptible
and resistant strains of the grain weevil(<u>Sitophilus granarius</u> L.). De-
hydrochlorination to 1,1-dichloro-2,2-bis(p-methoxyphenyl)ethylene
(MDE) occured. Bis(p-methoxyphenyl)acetic acid (MDA) also formed
(Rowlands and Lloyd, 1969).

The half-life of MeOCl in distilled water was estimated as 270 days.
In tap water which had contained fish, the half-life was 8 days (Merna
et al., 1972).

A heptane solution of methoxychlor was irradiated for 100 minutes at
310 nm. Nitrogen gas was constantly bubbled through the reaction mix-
ture. The solution separated on preparative TLC plate into five bands.
Analysis of the bands by mass spectra indicated the presence primari-
ly of the dichloro analog DME. In addition to unchanged methoxychlor,
methoxychlor olefin was also identified. There were indications of
traces of a methoxychlor isomer and a methoxybenzaldehyde. Two dimen-
sional chromatography of one band (the polar fraction) yielded six spots.
MS indicated these to be dimethoxybenzophenones, a methoxybenzoic
acid, and a methoxyphenol (MacNeil et al., 1972).
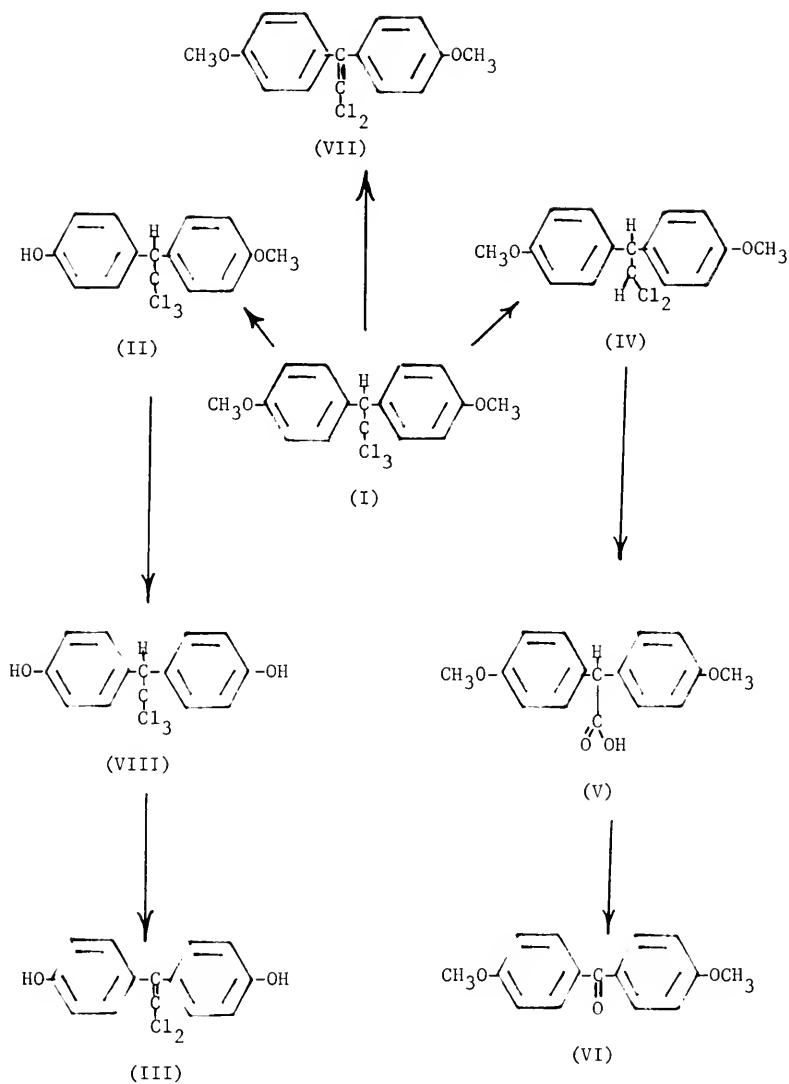
<u>N-Methyl-m-tert-butylphenyl carbamate</u>

The metabolism of this compound was studied with preparations from mouse liver, seven strains of houseflies (<u>Musca domestica</u>), blowflies (<u>Lucilia sericata</u>), grass grubs (<u>Costelytra zealandica</u>), bees (workers from an <u>Apis mellifera colony</u>), and meal worms (<u>Tenebrio</u> sp.). The same seven metabolites were observed with all species tested. Qualitative differences were observed. No aromatic ring hydroxylated metabolites were found. Hydroxylation did occur on the <u>t</u>-butyl and the <u>N</u>-methylcarbamoyl groups. The metabolites were identified as: m-<u>tert</u>-butylphenol(II); m-<u>tert</u>-butylphenylcarbamate(V); m-(β-hydroxy-<u>tert</u>-butyl)-phenol(III), -phenylcarbamate(VI), -phenyl <u>N</u>-methylcarbamate(VII), and -phenyl <u>N</u>-hydroxymethylcarbamate(VIII); and m-<u>tert</u>-butyl-phenyl— <u>N</u>-hydroxymethylcarbamate(IV) (Douch and Smith, 1971a).
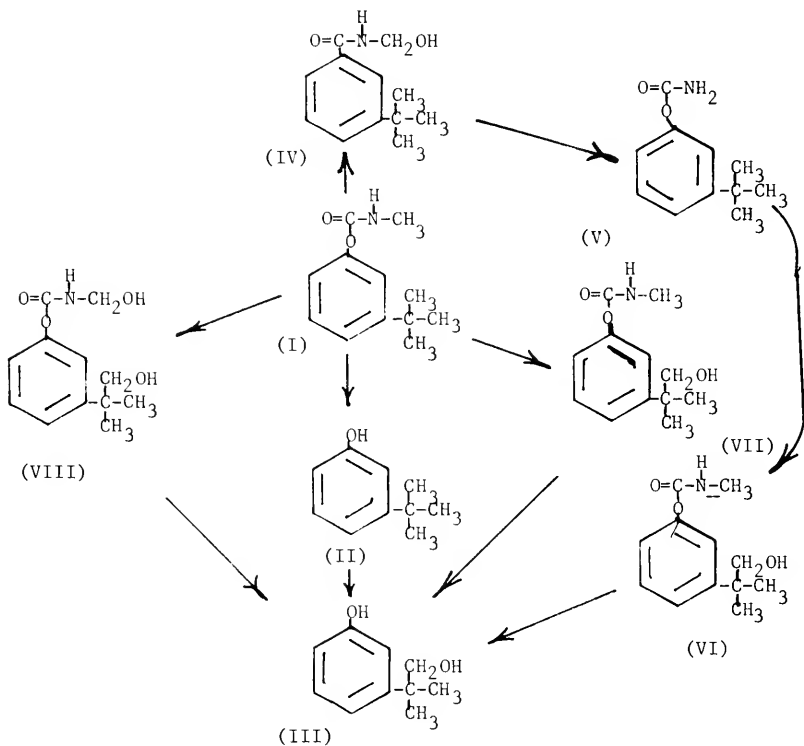
Methylenedioxy Compounds

Methylenedioxyphenyl compounds (MDP)

	R_1	R_2
Dihydrosafrole	$-H$	$-CH_2-CH_2-CH_3$
Isosafrole	$-H$	$-CH=CH-CH_3$
Myristicin	$-H$ $(3-CH_3O-)$	$-CH_2CH=CH_2$
Piperonal	$-CHO$	$-H$
Piperonyl alcohol	$-CH_2OH$	$-H$
Piperonyl butoxide	$-CH_2-CH_2-CH_3$	$-CH_2-(OC_2H_4)_2-O-C_4H_9$
Safrole	$-H$	$-CH_2-CH=CH_2$
Sulfoxide	$-H$	$-CH_2-CH-S-C_8-H_{17}$ CH_3O
Tropital	$-CH-[O-(C_2H_4O)-C_4H_9]_2$	$-H$

In mammals, MDP underwent degradation largely through oxidation of the methylene group to CO_2. Piperonyl butoxide, after administration to rats, was metabolized and eight compounds were excreted in the urine. Side chain oxidation occurred and the glycine conjugate of piperonylic acid was found in the urine. After administration of tropital to rats, N-piperonylglycine, the glucuronide and 3,4-dihydroxbenzoic acid were observed (Fishbein et al., 1969; Kamienski et al., 1970).

When piperonyl butoxide or isosafrole was incubated with rat liver microsomes, products were formed which exhibited an absorption spectrum similar to that of isocyanide with cytochrome P-450 of liver microsomes (Franklin, 1971). The metabolite-cytochrome P-450 complex formed rapidly but decomposed very slowly. The presence of this complex inhibited metabolism of piperonyl butoxide (Franklin, 1972).
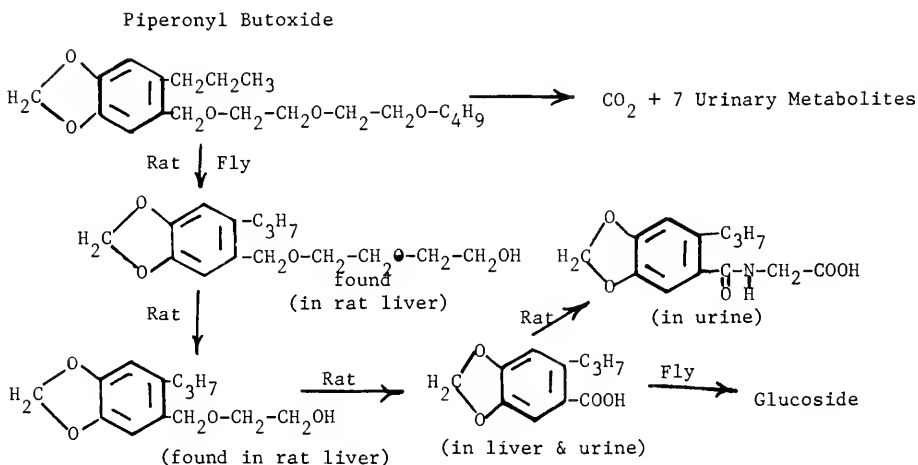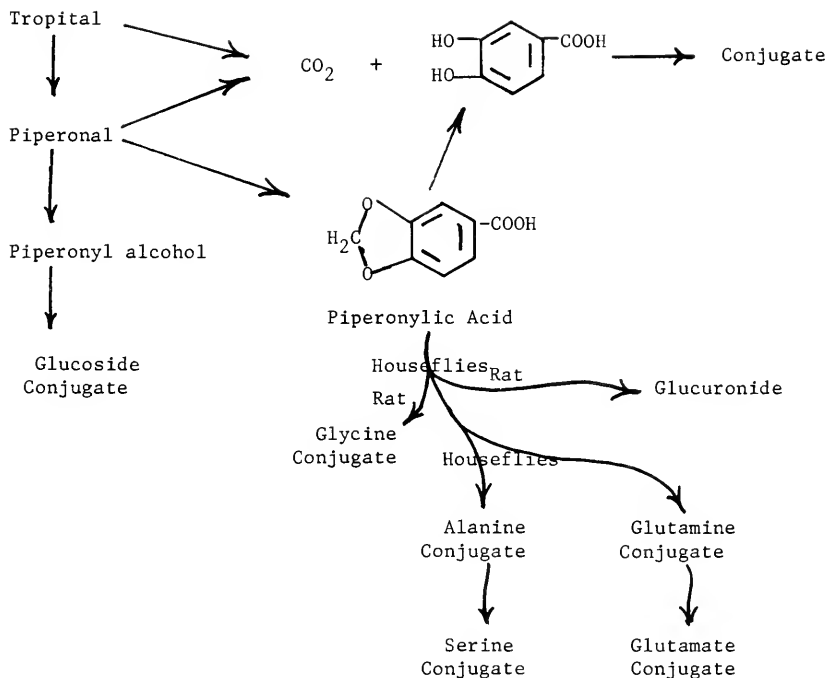
In houseflies, sulfoxide A & B underwent oxidation to the correspond-
ing sulfones and several unidentified compounds. Safrole and isosafrole
were converted to glycine, serine and glutamate conjugates of piper-
onylic acid. In other studies, in addition to these conjugates, con-
jugates of alanine and glutamine were seen after injection of piperonal,
piperonyl alcohol, safrole, and tropital into houseflies. The β-glu-
coside of piperonyl alcohol has also been found after injection of
tropital and piperonal into houseflies. The major amino acid involved
in conjugation of piperonylic acid apparently varied with the precursor:

Safrole or tropital	glycine
Piperonal or piperonylic acid	serine
Piperonyl alcohol	glutamate

In houseflies, $\underline{N}$-piperonylalanine was the precursor of the serine con-
jugate and $\underline{N}$-piperonylglutamine was the precursor of the glutamate
conjugate. Using labeled MDP, some $^{14}CO_2$ was also evolved (Esaac and
Casida, 1968 and 1969; Casida et al., 1968).

Piperonyl butoxide was metabolized by houseflies to eleven MDP analogs
and one catechol derivative. One metabolite chromatographed with the
glucoside of 6-propylpiperonylic. Another was characterized as the
glucoside-6-phosphate of 6-propylpiperonylic acid. Other metabolites
were identified as indicated in the tentative metabolic pathway
(Esaac and Casida, 1969).

Piperonyl butoxide is stable at $100^{O}C$ and thin films of commercial grade
material was stable during exposure to intense fluorescent light for
periods up to seven days (Friedman and Epstein, 1970).

The effect of UV light on safrole and piperonyl butoxide is summarized
in the diagrams (Fishbein and Gaibel, 1971).

Cell-free extracts of a Pseudomonas fluorescens strain metabolized
3,4-methylenedioxybenzoate to protocatechuate and formate. The methylene
carbon was hydroxylated to the unstable hydroxymethylenedioxy analog.
This, in turn underwent hydrolysis to formate and the dihydroxybenzoate.
Pyrocatechuate, isolated and identified by m.p. and IR and UV spectro-
photometry as an intermediate, was metabolized to 3-oxoadipate (Buswell,
1972b; Buswell and Mahmood, 1972).

Safrole $\xrightarrow[\text{Quartz, Benzene, 18 days}]{\text{450 W Hanovia Hg Lamp}}$

(90%)
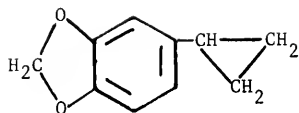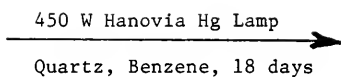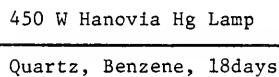
Piperonyl Butoxide $\xrightarrow[\text{Quartz, Benzene, 18days}]{\text{450 W Hanovia Hg Lamp}}$ Butyl carbitol

+

Ethylene glycol + 2-Propyl

4,5-methylenedioxytoluene
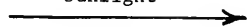
$\xrightarrow[\text{1 week}]{\text{Sunlight}}$ Polymers + 2 Unknowns

2,3-Methylenedioxynaphthalene (MDN)

When houseflies and mice were exposed to MDN, the enormous quantitative
differences in oxidation of this synergist accounted for the selectivity
when combined with carbaryl. In mice, this product was completely
degraded within 12 hours; but it was scarcely degraded in 24 hours in
houseflies. Minor qualitiative differences were observed, primarily
in the nature of the conjugating sugars, between houseflies and mice
(Sacher et al., 1969).

% Conversion of metabolites in mice (M) and in houseflies(F);
Glu = Glucuronide in mice and Glucoside in houseflies.
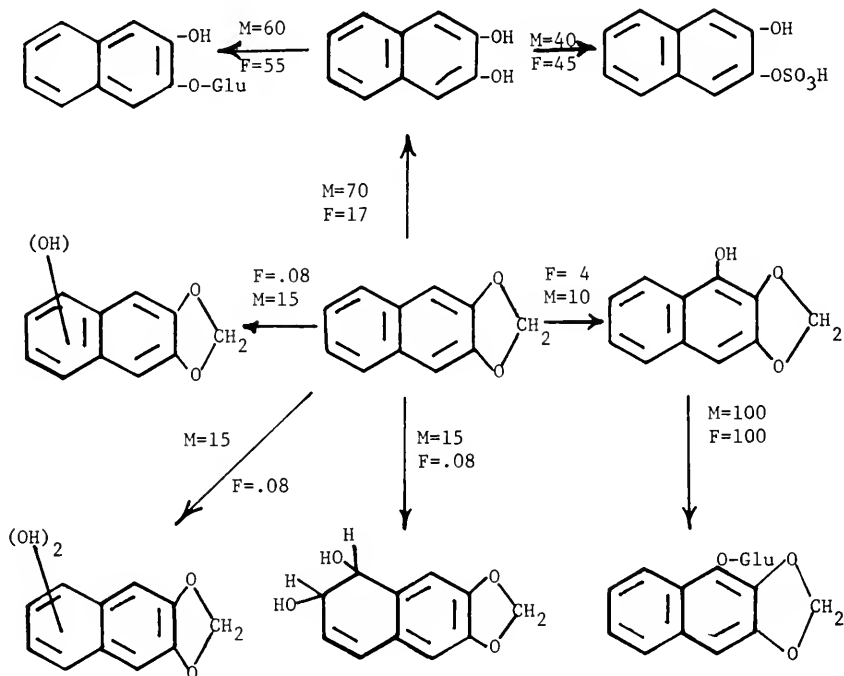
<u>MEVINPHOS</u> (Phosdrin) [Methyl-3-(dimethoxyphosphinyloxy)crotonate]

<u>Cis</u>-isomer of mevinphos was degraded by mammalian liver supernatant protein (100000g). The <u>trans</u>-mevinphos was cleaved by cleavage at the P-O-vinyl bond (Hutson et al., 1972).

MIREX (GC-1283) [Dodecachlorooctahydro-1,3,4-metheno-2H-cyclobuta [c,d] pentalene]

When a single dose of mirex was orally administered to rats, 58.5% of the mirex - ^{14}C was excreted in the feces and 0.69% in the urine after 7 days. Tissue storage reached 27.8 ppm in fat in the same time. No metabolites were detected nor were any detected after mirex incubation with preparations from rat, mouse, and rabbit livers and plant roots. Pea and bean plant roots concentrated mirex; and small amounts were translocated to aerial parts when plants grew for 2 days in water containing 1 to 10 ppm mirex (Mehendale et al., 1972).

Mirex deposits on silica gel were exposed in the environment for periods up to 3 months. A monodechloro product was isolated and found to be either a or b (Gibson et al., 1972).

(a)

(b)
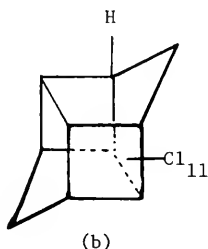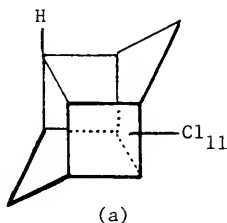
Two groups of male rats were administered labeled Mobam by stomach tube. Urine and feces were collected daily. After three days, less than 1% of the label remained in the tissues. After extraction and chromatography, 4-hydroxybenzothiophene was recovered as the glucuronide and as the sulfate. Four other metabolites were found but not identified (Robbins et al., 1969).

After administration of ^{14}C-Mobam to dairy goats and a lactating cow, two metabolites were found in the urine: 4-benzothienyl sulfate and 4-benzothienyl sulfate-1-oxide. These accounted for about 90% of the ^{14}C excreted in the urine. In milk, the oxide accounted for over 95% of the radioactivity present. The glucuronide was not found in these studies. Several other metabolites were not identified. The expired air indicated hydrolysis and metabolism of the carbamate ester. 75% of the carbonyl-^{14}C and 38% of the methyl-^{14}C were exhaled as ^{14}CO within 24 hours (Robbins et al., 1970).

Mobam, ^{14}C-labeled in the ring, carbonyl/or methyl position, was incubated with rumen bacterial cultures. Strains of the genera Anaerovibrio, Bacteroides, Butyrivibrio, Eubacterium, Lachnospira and Ruminococcus were demonstrated to degrade Mobam. Carbonyl-^{14}C gave rise to ^{14}CO$_2$. Mobam was also metabolized to 4-HO-benzothiophene (Williams and Robbins, 1969; Williams and Stolzenberg, 1972).
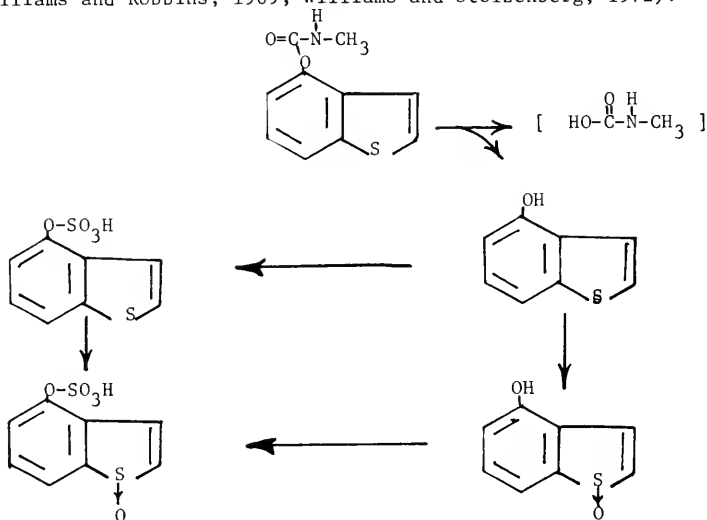
Bean and corn plants were grown in soil treated with labeled
mocap. Only a small fraction of the labeled mocap was taken
up from the soil and only a portion of this was extractable from
the bean and corn plants. Most of the radioactivity remained in
the soil. After chloroform extraction and chromatography, five
peaks were observed. Further analyses established the identity
of three compounds: ethyl sulfide, methyl propyl sulfide, propyl
disulfide. The other two compounds could not be isolated in
sufficient quantities for definitive characterization. However,
these compounds cochromatographed on thin-layer plates and silic
acid columns with ethyl propyl sulfone and ethyl propyl sulfoxide.

In the methanol-water extract of the treated soil, a significant
portion of the activity was present in the form of hydrolytic
products. S-propyl phosphorothioic acid, $\underline{O}$-ethyl-$\underline{S}$-propyl
phosphorothioic acid, and O-ethyl phosphoric acid were identified.
In addition to the latter two compounds, desethyl mocap and methyl
propyl sulfide were formed by rats after exposure to mocap
(Menzer et al., 1971).

After administration of labeled mocap, by stomach tube to rats,
urine contained traces of methyl propyl sulfide, methyl propyl
sulfoxide, and methyl propyl sulfone in the chloroform soluble
portion. The major water-soluble metabolite was $\underline{O}$-ethyl-$\underline{S}$-propyl
phosphorothioic acid. This was also obtained with liver microsomes
and supernatant. Rat urine also contained $\underline{O}$-ethyl phosphoric acid,
$\underline{S}$-propyl phosphorothiolic acid and $\underline{S}$,$\underline{S}$-dipropyl phosphorodithioic
acid. Rat and rabbit liver supernatant enzymes de-ethylated Mocap
in the presence of glutathione and formed $\underline{S}$-ethylglutathione
(Iqbal and Menzer, 1972).
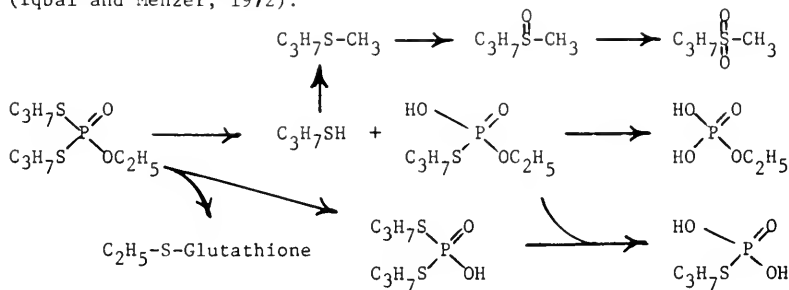
MORESTAN [6-Methyl-2,3-quinoxalinedithiol cyclic S,S-dithiocarbamate]

The major metabolite on and in peels of apples, oranges and cucumbers
has been identified as 6-methyl-2,3-quinoxalinedithiol (Flint and
Gronberg, 1971).
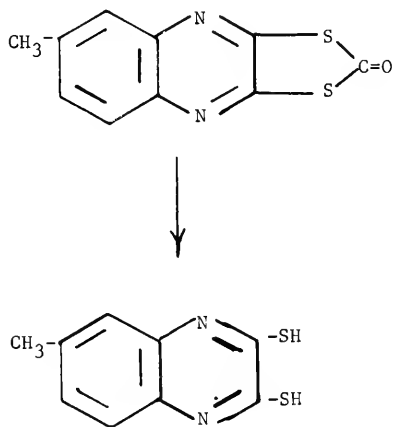
<u>1-Naphthaleneacetic Acid</u> (NAA)

A metabolic product of naphthaleneacetic acid from wheat coleoptils
was identified as the 5-hydroxy analog (Legler et al., 1965). After
exposure of apple leaves to NAA, 10% was absorbed, 10% remained on
the leaf surface, and 80% was lost. Two unidentified water-soluble
products were formed after absorption. On the leaf, UV radiation
degraded NAA with loss of the carboxyl group (Luckwill and Lloyd-
Jones, 1962).

When an aqueous solution of NAA was irradiated at 253.7 nm, a series
of compounds were observed: 1-naphthaldehyde, 1-naphthylenemethanol,
1-naphthoic acid, 1-methylnaphthalene, naphthalene, and phthalic acid.
In ethanolic solution, in addition to phthalic acid, ethyl 1-naphthoate
and NAA ethyl ester were also produced (Watkins, 1969; Crosby and Tang,
1969).

NELLITE [N,N'-Dimethyl phenylphosphorodiamidate]

Labeled nellite was applied to a furrow in which cottonseed was planted. Soil was sampled over a period of 406 days and a linear regression equation was calculated:

$$\mu g = 948-(4.2)(\text{Number days}).$$

The standard error of the estimate is 25 and the standard error of the regression coefficient is 0.2. Soil extracts contained dihydrogen phenylphosphoric acid and hydrogen phenyl N-methylphosphoramidate (Meikle and Christie, 1969).

NEMACIDE [O-(2,4-Dichlorophenyl)-O,O-diethyl phosphorothioate]

When nemacide was fed to laying hens, residues of nemacide were
found in the liver, muscle, fat and yolk. The metabolite 2,4-
dichlorophenol was found in liver and yolk. At a feeding level
of 800 ppm of nemacide in the diet, eggs from treated hens had
an undesirable flavor (Sherman et al., 1971 and 1972).

NEMACUR [N-Isopropyl-O-ethyl-4-methylthio-m-tolylphosphoramidate]

^{14}C- and ^{3}H-labeled nemacur was injected into the stems of beans, tomatoes, peanuts and potatoes and harvested up to 28 days later. The sulfoxide and sulfone were isolated and identified as the main metabolites. Some of the corresponding free phenols were also observed. Several additional metabolites were detected but not identified (Waggoner, 1972).

<u>NIAGARA 10637</u> [Ethyl propylphosphonate]

When exposed to oxygen in combination with a reduced metal ion, ethyl propylphosphonate generates ethylene and propylene (Dollwet and Kumamota, 1970).

Nicotine [1-Methyl-2-(3-pyridyl)pyrrolidine]

When (-)nicotine-1[1]-oxide was administered orally to a man, (-)nicotine and (-)cotinine were formed in the intestine and excreted in urine (Beckett et al., 1970).

After intravenous injection of nicotine into a cat, cotinine formed very rapidly. Pooled urine contained in addition to nicotine and cotinine, nornicotine, demethylnicotine, pyridylacetate, nicotine-1[1]-oxide and γ-oxo-γ-(3-pyridyl)-N-methylbutyramide (Turner, 1969).

Homogenates of hamster liver are two or three times more effective in degrading nicotine than those from rat liver. Hamsters synthesize 6 to 10 times more cotinine than do rats. Demethylation and oxidation occurred on incubation with liver homogenates (Harke et al., 1970).

Guinea-pig and rabbit liver formed both isomers of nicotine-1[1]-oxide. Mouse and hamster liver and guinea-pig lung produced mainly the levo-rotary isomer. Both isomers were identified in the urine of cigarette smokers (Booth and Boyland, 1970).

In other studies nicotine was oxidized by NADPH and oxygen dependent mixed function oxidases of guinea-pig tissues to two optically active isomers of nicotine-1[1]-oxide and to cotinine. Aerobically no further metabolism occurred. Anaerobically the oxides are reduced to nicotine (Booth and Boyland, 1971).

Observed metabolic and stereochemical variations in nicotine metabolism between species was considerable. Hepatic preparations from guinea-pigs formed twice as much cotinine from (-)-nicotine as from (+)-nicotine and rabbit hepatic preparations formed more cotinine and N-oxide from (-)-nicotine than from (+)-nicotine. While cotinine formation pre-dominated in the rabbit, N-oxidation was the principal metabolic route in the guinea-pig. When hamster homogenates were used, (-)-nicotine yielded more cotinine than N-oxide whereas (+)-nicotine yielded more N-oxide than cotinine, Mouse hepatic preparations yielded more N-oxide from (+)-nicotine than from (-)-nicotine. While the ratio of trans/cis nicotine-1[1]-N-oxide varied considerably between species, the cis diaster-eoisomers predominated from (-)-nicotine and the trans isomer from (+)-nicotine except in rabbit hepatic prepartions. In the latter, the cis diastereoisomer predominated from both isomers of nicotine. No sex differences were observed (Jenner et al., 1971).

After absorption through stems of excised leaves of Nicotiana glutinosa, nicotine-1[1]-oxide was converted to nicotine and nornicotine. Nornicotine formation approximated the conversion of nicotine to nornicotine (Alworth et al., 1969).

Isomethonium ion   Nicotine   Oxynicotine

N-CH$_3$-Myosmine   6-HO-N-CH$_3$-Myosmine   6-HO-N-CH$_3$-Myosmine   6-HO-Nicotine

Pseudooxynicotine

6-HO-Pseudooxynicotine

3-Succinoylpyridine

3-Succinoyl-pyridone-6

2,6-Dihydroxy-pyridine

2,6-Dihydroxy-pseudo-oxynicotine

2,6-Dihydroxy-N-methyl-myosmine

2,3,6-Trihydroxy-pyridine

CO$_2$+NH$_3$+ dibasic acids   Blue Pigment

273
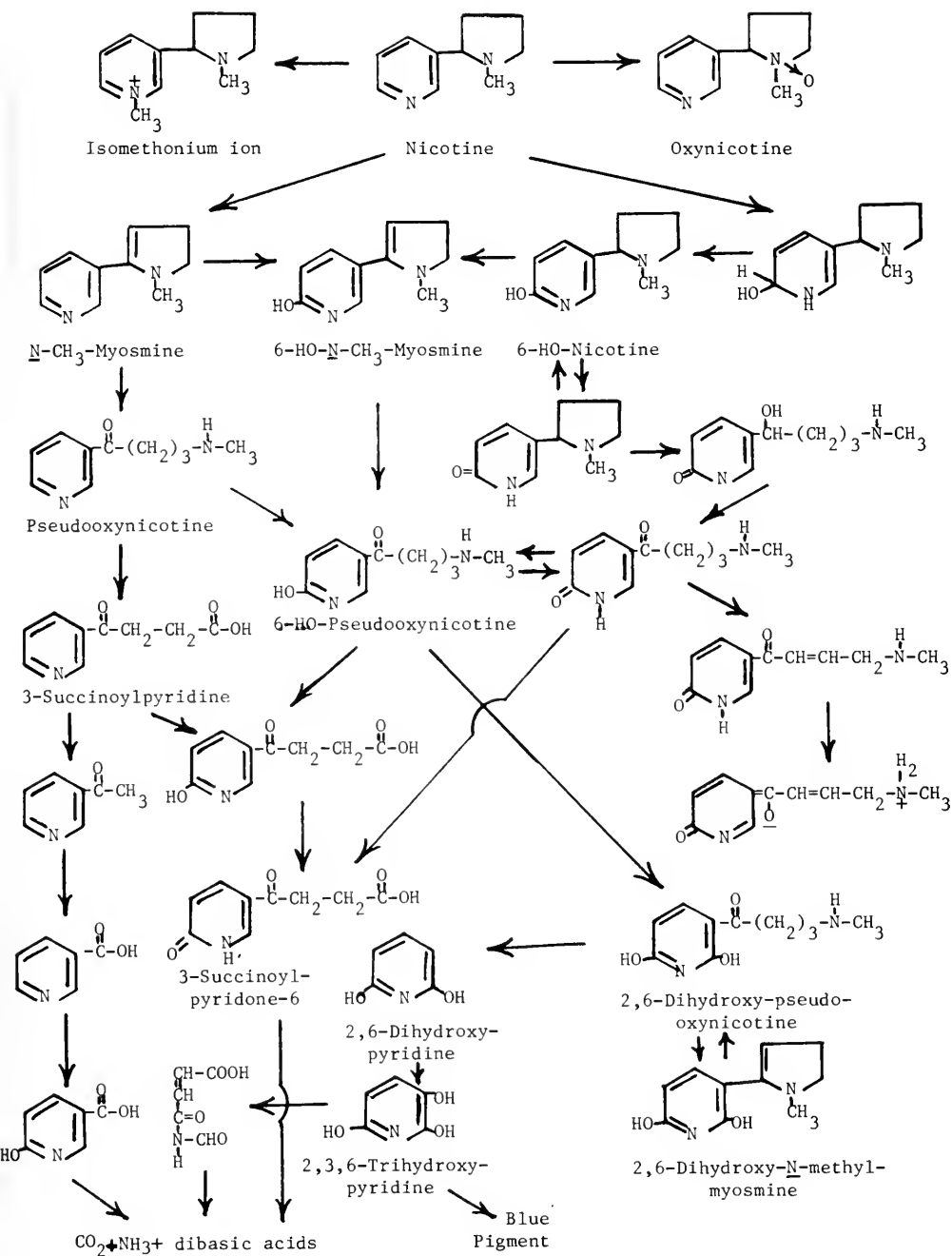
A bacterial strain, isolated from tobacco leaves, oxidized nicotine to γ-aminobutyric acid (Casida and Rosenfield, 1958). Arthrobacter oxydans, adapted to L-, D-, DL-nicotine, converted both nicotine isomers initially to the 6-hydroxy nicotine. These were then metabolized to the same compound, 6-hydroxy-N-methylmyosmin. The latter was successively converted to 3-(4-methylaminobutan-1-one)-6-hydroxypyridine and 2,6-dihydroxy-3-(4-methylaminobutan-1-one)-pyridine (Decker and Bleeg, 1965; Decker and Dai, 1967; Gherna et al., 1965; and Gries et al., 1961a).

After adaptation the first two enzymes of nicotine degradation in A. oxidans were subject to induction and repression by some growth substances. Cells grown on L-nicotine synthesized L-6-hydroxynicotine oxygenase whereas cells grown on D-nicotine synthesized both D- and L-enzymes (Decker and Bleeg, 1965). The oxidase was found to be an FAD-protein. In the presence of a cell free extract or intact cells, N-methylmyosmine and nicotine gave rise to the same products. An OH group was introduced into the 6-position of both. It appeared, therefore that 6-hydroxy-N-methlmyosmine was an intermediate and the ketone was formed by hydrolysis (Decker et al., 1960; Decker and Dai, 1967).

When grown on L-nicotine, Arthrobacter oxydans produced a blue pigment in the presence of oxygen. When degradation was blocked, the unstable propyl ketone lead to a tautomer. Degradation of nicotine by A. oxydans has been summarized (Decker et al., 1961a and 1961b; Eberwein et al., 1961; Gries et al., 1961a and 1961b).

Early studies indicated that fermentation of nicotine produced methylamine as a degradation product but not pyridine (Weber, 1935). In other fermentation studies, 3-pyridyl methyl ketone, 2,3^1-dipyridyl, oxynicotine, nicotinic acid, and some unidentified matrials were found (Frankenburg et al., 1952). Nicotine degradation products formed during fermentation included 3-pyridyl propyl ketone, nicotinamide and N-methylnicotinamide (Frankenburg et al., 1955).

Nicotine-degrading microorganisms were obtained from tobacco seeds. It was found that degradation of nicotine could proceed along three different pathways. Path #1 started with hydroxylation to form 6-hydroxynicotine. Further degradation produced a product not identified but believed to be an α-(N-methylpyrrolidine) glutaconic acid. This degraded to methylamine, ammonia, oxalic acid, and traces of malonic and succinic acids. The other two paths procede similarly through γ-methylaminopropyl-3-pyridyl ketone, 3-pyridyl propyl ketone, and γ-keto-γ-(3-pyridyl)-butyric acid. Then they diverge and procede via 3-succinoyl-6-hydroxypyridine and a glutaconic acid derivative to methylamine, ammonia, oxalate, malonate and succinate or via 3-pyridyl methyl ketone, nicotinic acid, 6-hydroxynicotinic acid and a glutaconic dialdehyde derivative (Frankenberg and Vaitekunas, 1955).

Bacterial Degradation Of Nicotine

Nicotine → 6-Hydroxynicotine → 6-Hydroxy-N-methylmyosmine

6-Hydroxy-pseudooxynicotine

2,6-Dihydroxy-pseudo-oxynicotine

γ-Methylaminobutyric acid $CH_3-N-(CH_2)_3-C-OH$

2,6-Dihydroxy-pyridine

2,6-Dihydroxy-N-methylmyosmine

Non-enzymatic

2,3,6-Trihydroxy-pyridine

Blue Pigment I

Pigment II

Pigment III

NH_4OAc
$130^\circ C$

2-Hydroxypyridine

Maleamic acid → Maleic acid → Fumaric acid

1= A. oxydans
2= A. nicotinovorum
3= A. crystallopoietes

A soil bacillus which used nicotinic acid as a soil nitrogen source produced a soluble blue pigment. Oxidation proceded via 6-hydroxy- and 2,6-dihydroxy-nicotinic acid. It was suggested that metabolism also involved decarboxylation to 2,3,6-trihydroxypyridine followed by ring rupture and formation of maleamic acid. Some 2,6-dihydroxypyridine was formed non-enzymatically (Ensign and Rittenberg, 1964).

Incubation of 6-hydroxypseudooxynicotine, 6-hydroxynicotine or nicotine with cell free extracts of a soil bacterium produced a compound identified as 2,6-dihydroxy-N-methylmyosmine. Other studies indicated that 2,6-dihydroxypseuodooxynicotine was the intermediate (Richardson and Rittenberg, 1961a and 1969b). An enzyme fraction of A. oxidans anaerobically cleaved 2,6-dihydroxypseudooxynicotine. The compounds, also derived from 6-hydroxypseudooxynicotine, were identified as 2,6-dihydroxy-pyridine and γ-methylaminobutyric acid. Further oxidation of the dihydroxypyridine yielded the blue pigment or proceeded through maleamic acid, maleic acid and fumaric acid (Gherna et al., 1965).

Arthrobacter nicotinovorum, when grown in the presence of nicotine, produced a blue to violet pigment referred to as Nicotine-blue. After isolation, this pigment was characterized as a magnesium "azaquinone" (Niemer et al., 1964). Cornybacterium insidiosum, Arthrobacter atrocyaneus, Pseudomonas indigofera and Arthrobacter crystallopoietes produce related pigments which are similar to that of A. nicotinovorum (Kuhn et al., 1964). The bronze-green pigment of A. crystallopoietes formed from 2-hydroxypyridine and is identical to the mono-potassium salt of I.

Nicotine

Polymeric pyridine
compounds

Polymeric Pyridine
compounds
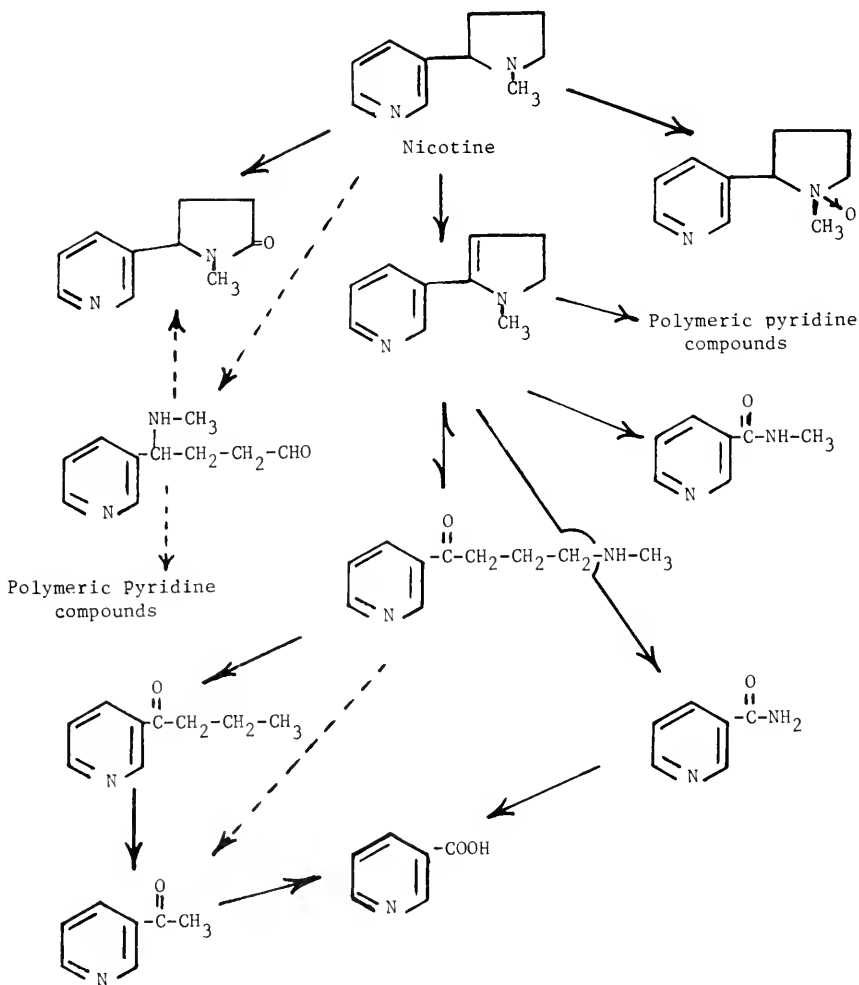
DCNB   [3,4-Dichloronitrobenzene]

Pigeons metabolized DCNB mainly by reduction of the nitro group.
Only trace amounts of mercapturic acid, formed by replacement of
the 4-Cl, was produced (Wit and Leeuwangh, 1969).

TCNB   [2,3,5,6-Tetrachloronitrobenzene]

TCNB was metabolized to the mercapturic acid only with removal of
the nitro group (Wit and Leeuwangh, 1969).

N-Serve [2-Chloro-6-trichloromethylpyridine]

When incubated with fertile garden soils, N-Serve persisted for more
than 278 days under aerobic conditions (Naik et al., 1972).

NTA-^{14}C was administered orally to rats. Ninety-five percent was excreted in the urine. Less than 1% was excreted as CO_2. Absorption of NTA from the GI tract varied: dog>rat>rabbit≅monkey. NTA-^{14}C was found to be deposited in the skeleton. The concentration tended to increase with the number of administered doses. The most active areas for accumulation were at the sites of very active bone formation. Although the concentration decreased rapidly with cessation of intake, a small amount was retained in the bone after each dose (Michael and Wakim, 1971).

In an aerated sewage lagoon, trisodium NTA breakdown was temperature dependent: 93% at 15°C; 47% at 5°C; and 22% at 0.5^{o}C (Rudd and Hamilton, 1972).

Washed cell suspension of Pseudomonas sp., isolated from sewage effluent, degraded all NTA-nitrogen to ammonium prior to total conversion of the NTA to CO_2 and water. Small amounts of nitrite were also formed. The study tended to support the contention that NTA degradation proceeded through aminodiacetic acid and glycine (Focht and Joseph, 1971).

A study of the photochemistry of ferric NTA complexes was undertaken and irradiation characteristic of sunlight was used. In addition to formaldehyde, CO_2 and iminodiacetic acid (IDA) were formed (Trott et al., 1972).

OXYCARBOXIN [2,3-Dihydro-5-carboxanilido-6-methyl-1,4-oxathiin-4,4-
           dioxide]

In hydroponic solutions, in which beans were grown, oxathiin(I)
underwent rapid degradation and the products were translocated
into the plants. Three major products have been identified as:
2-(vinylsulfonyl)acetanilide(II); 4-phenyl-3-thiomorpholinone-4,4-
dioxide(III); 2-(2-hydroxyethylsulfonyl)acetanilide(IV). Compound II
was also obtained by refluxing oxycarboxin in methanol; compound III,
by refluxing oxycarboxin in pH 8 aqueous buffer; compound IV, by
treating oxycarboxin with pH 10 buffer (Ross et al., 1972).
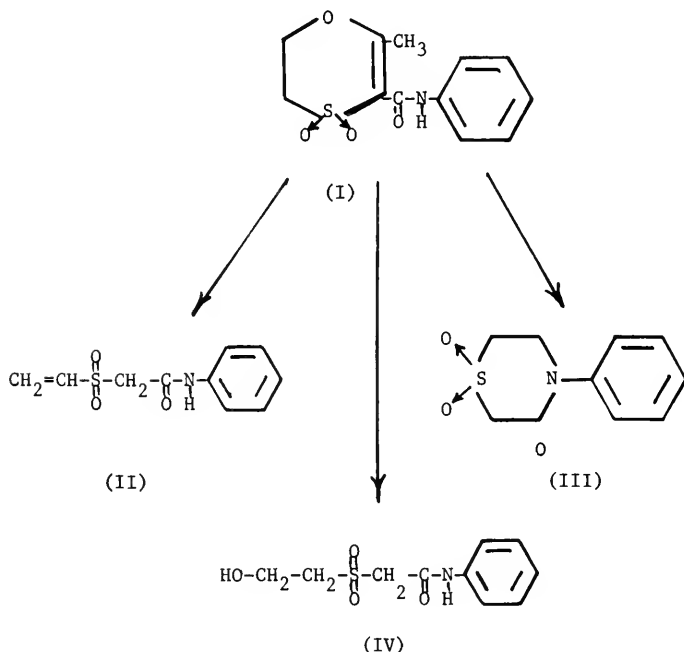
ETHYL PARATHION   [O,O-Diethyl p-nitrophenyl phosphorothioate]

METHYL PARATHION   [O,O-Dimethyl p-nitrophenyl phosphorothioate]

Field workers exposed to parathion exhibited varying degress of cholinesterase depression. Analyses of blood and urine samples showed the presence of parathion and p-nitrophenol, respectively (Roan et al., 1969).

Rats orally administered labeled ethyl parathion, initially converted parathion to paraoxon and to diethyl phosphorothioic acid. Inorganic sulfur was excreted as sulfate. Other urinary metabolites observed were phosphoric acid, O-ethyl-phorothioic acid, diethyl phosphoric acid, and desethyl paraoxon. One metabolite was not identified (Appleton and Nakatsugawa, 1972; Nakatsugawa et al., 1969).

$^{14}CH_3$-labeled methyl paraoxon was metabolized by homogenates of mouse liver. Addition of glutathione greatly stimulated the reaction. S-methylglutathione and O-methyl paraoxon were produced in equimolar concentrations. When rats were administered methyl parathion, dimethyl phosphoric acid was excreted in the urine together with O-methyl and O,O-dimethyl paraoxon and three un- identified compounds (Hollingworth, 1969).

In in vitro studies with rabbit liver microsomes, it was determined that oxygen from $^{18}O_2$ was retained in paraoxon and diethylphosphate but not in diethylphosphorothioate. When the reaction was conducted with $H_2^{18}O$, the label was found in diethylphosphorothioate (Ptashne et al., 1971). Other studies indicated that parathion had multiple binding sites on cytochrome P-450 (Roth and Neal, 1972).

The metabolism of parathion by rabbit lung and liver tissues was compared. Liver tissue converted parathion to diethyl phosphorothioic acid and paraoxon at the rate 0.6 and 1.4 μ moles/min., respectively; in lung tissue this rate was 0.007 and 0.015 μ moles/min. (Neal, 1972).

Rabbit liver microsomes were incubated with a series of dialkyl p-nitrophenyl phosphorothioates. The K_m and V_{max} was determined for formation of corresponding dialkyl p-nitrophenyl phosphates and dialkylphosphorothioates (Wolcott et al., 1972).

Metabolism to Oxon Analog

Alkyl Group	V_{max} (n moles/20 min/ mg Protein)	K_m ($M \times 10^{-5}$)
Methyl	11.5 ± .3	0.71 ± .08
Ethyl	12.6 ± .4	3.10 ± .23
Propyl	14.9 ± .6	1.76 ± .21
Butyl	14.9 ± .6	1.37 ± .17

Metabolism to Dialkyl Phosphorothioate and Phenol

Alkyl Group	V_{max} (n moles/20 min/ mg Protein)	K_m ($M \times 10^{-5}$)
Methyl	7.9 ± .2	0.95 ± 0.09
Ethyl	7.7 ± .2	1.12 ± .09
Propyl	6.3 ± .2	1.40 ± .15
Butyl	2.9 ± .1	1.16 ± .16

Similar studies were conducted with a series of phenyl substituted diethyl phenylphosphorothioates (Wolcott and Neal, 1972).

Metabolism to Oxon Analog

Phenyl Substituent	V_{max} (n moles/20 min/ mg Protein)	K_m ($M \times 10^{-5}$)
$p-NO_2$	15.94 ± 1.73	3.18 ± 1.75
$m-NO_2$	15.63 ± .41	2.02 ± .28
$m-CF_3$	7.94 ± .37	4.82 ± .72
$p-Cl$	7.35 ± .10	2.70 ± .17
Unsubstituted	9.04 ± .18	2.44 ± .22
$m-CH_3$	8.53 ± .34	6.93 ± .90
$p-CH_3$	7.23 ± .53	6.89 ± 1.38
$p-OCH_3$	7.78 ± .40	3.16 ± .63

Metabolism to Dialkyl Phosphorothioate and Phenol

Alkyl Group	V_{max} (n moles/20 min/ mg Protein)	K_m (M x 10^{-5})
p-NO_2	6.59 $\pm$ 0.52	2.25 $\pm$ 0.90
m-NO_2	7.14 $\pm$ .31	2.77 $\pm$ 0.53
m-CF_3	3.15 $\pm$ .36	6.63 $\pm$ 2.07
p-Cl	3.85 $\pm$ .14	1.95 $\pm$ 0.39
Unsubstituted	4.45 $\pm$ .45	5.47 $\pm$ 1.59
m-CH_3	5.69 $\pm$ .27	7.92 $\pm$ 3.63
p-OCH_3	4.12 $\pm$ .25	2.57 $\pm$ 0.69

When white mice were orally administered isopropyl parathion, two
metabolites observed in the urine were believed to be the monoisopropyl
analogs of parathion and paraoxon. Isopropyl paraoxon and diisopropyl
phosphorothioate were also observed (Camp et al., 1969).

p-Aminophenol, which arises from cleavage of the P-O bond, was metabolized
by the clonal MH_1C_1-strain of rat hepatoma cells via glucuronide formation
(Dybing and Rugstad, 1972).

Recent studies indicated that freshwater fishes contain mixed function
oxidase enzymes capable of activating parathion (Ludke et al., 1972).

Houseflies (Musca domestica L.) metabolized ethyl parathion by two
routes: cleavage of the P-O bond to give diethyl phosphorothioic
acid; and by activation to the P=O analog with formation of inorganic
sulfate (Nakatsugawa et al., 1969). Paraoxon injected into a
susceptible strain was degraded by desethylation as well as by cleavage
of the P-O bond to form diethyl phosphate (Nolan and O'Brien, 1970).

Studies indicated that glutathione-dependent degradation of parathion
confers a little resistance to houseflies. Three products were
formed from ethyl-labeled parathion and identified as ethylglutathione,
diethyl phosphorothioic acid and desethylparathion (Oppenoorth et al.,
1972).

Labeled paraoxon was incubated with homogenates and cell fractions
of two resistant strains of houseflies. Diethylphosphate was the
main product. Some acetic acid and an unidentified product were
also observed (Welling et al., 1971).

The southern armyworm (Prodenia eridania) converted 17-25% of orally administered p-nitrophenol to the sulfate ester within 48 hours. A considerable amount of p-nitrophenol was bound with plant pigments which were derived presumably from the ingested bean plant. These materials were not glucosides or phosphates but were not further characterized (Yang and Wilkinson, 1971).

Isopropyl parathion metabolism was qualitatively the same in houseflies and honey bees but differed quantitatively. Diisopropyl phosphorothioic acid, isopropyl paraoxon and O-isopropyl parathion were observed (Camp et al., 1969).

When Chlorella pyrenoidosa proteose was incubated with ethyl parathion, the major metabolite was aminoparathion. Three unidentified metabolites were also present (Zuckerman et al., 1970).

In lake bottom sediments, parathion was reduced to aminoparathion under aerobic and anaerobic conditions. However, under aerobic conditions, oxidation to other metabolites apparently occurred. Chemical hydrolysis in lake waters was pH dependent (Graetz et al., 1970).

When incubated with Rhizobium japonicum and R. meliloti, 85% of the parathion was metabolized to aminoparathion and about 10% was hydrolyzed with formation of O,O-diethyl phosphorothioate. No paraoxon was detected (Mick and Dahm, 1970).

Parathion was applied three times at the rate of 1.5 and 0.5 lb/acre to field tabacco. Maximum time to zero residue level was estimated to be seven days (Keil et al., 1971).

The reaction of parathion with peroxytrifluoroacetic acid gave diethyl phosphorothioic acid, paraoxon, and tetraethyl pyrophosphate (Ptashne and Neal, 1972).

PCNB (Terraclor) [Pentachloronitrobenzene]

PCNB was fed to beagle dogs for up to 2 years. Analyses of feces
showed the formation primarily of pentachloroaniline (PCA).
Small amounts of pentachlorobenzene (PCB), hexachlorobenzene (HCB),
and methyl pentachlorophenyl sulfide were also found. In young
cotton plants planted in soil treated with PCNB, in addition to
the foregoing, 2,3,4,5-tetrachloronitrobenzene was also observed
(Kuchar et al., 1969).

In milk from cows treated with PCNB, traces of PCNB were observed
in addition to pentachloroaniline and methyl pentachlorophenyl
sulfide (Borzelleca et al., 1971).

PCNB was incubated with sensitive and resistant fungi. The
sensitive fungi, two isolates of Rhizoctonia solani, absorbed
much greater quantities of PCNB than did the resistant fungi,
Fusarium oxysporum f. lycopersici and Fusarium oxysporum f.
niveum. The latter, however, excreted greater quantities of
the two identified metabolites--pentachloroaniline and pentachloro-
thioanisol--from the mycelium into the culture medium than did the
R. solani (Nakanishi and Oku, 1969).

When PCNB was irradiated at 2537Å in hexane, four products were
identified: 1,2,4,5-tetrachlorobenzene, pentachlorobenzene, 2,3,4,
5-and 2,3,4,6-tetrachlorobenzene (Crosby and Hamadmad, 1971).

In moist soil, PCNB was converted to PCA (pentachloroaniline)
which was stable (Ko and Farley, 1969).

PCA

PCNB

HCB
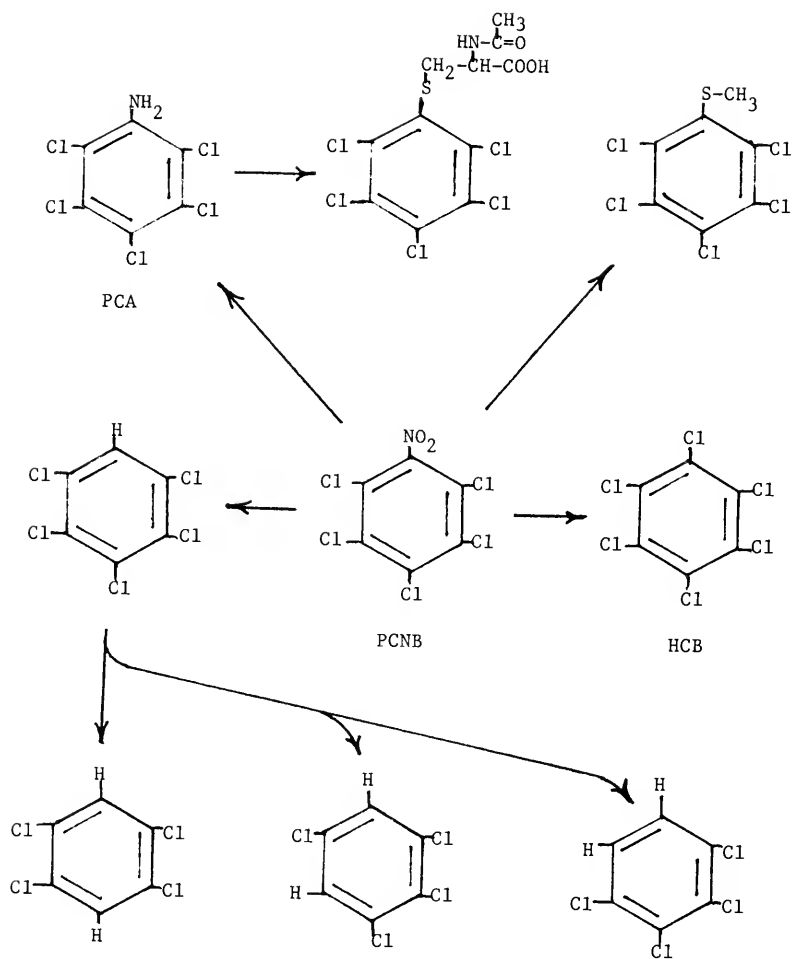
PCP   [Pentachlorophenol]

In the urine of a rabbit orally administered PCP-Na, pentachloro-
phenyl β-glucuronide and chloranil were found. Chloranil was also
observed in internal organs of mice two hours after intraperitoneal
injection (Tashiro et al., 1970).

^{14}C-PCP was administered to mice by subcutaneous or intraperitoneal
injection. Most of the activity (72-83%) was excreted in the urine
in four days; about half, in 24 hours; and only a trace (0.05%), in
expired air. High activity was observed in gall bladder and its
contents, wall of stomach fundus, contents of G.I. tract, and liver.
In the urine, in addition to unchanged PCP, about 8% of activity
was in the form of a PCP conjugate, not further identified. Tetra-
chlorohydroquinone (TCH) was also detected (Jakobson and Yllner, 1971).

In shellfish (Tapes philippinarum) PCP was rapidly absorbed and dis-
tributed into various tissues; and then it was quickly eliminated.
Most of the accumulated PCP in tissues was undecomposed and either
free or in bound form. The bound form was identified as the sulfate
ester of PCP (Kobayashi et al., 1969, 1970a, 1970b).

The protoporphyrin enzyme peroxidase, detected in snails, catalyzed
oxidation of PCP to 2,2',3,3',5,5'6,6',-octachlorobiphenylquinone.
In vitro studies with horseradish peroxidase also produced this
compound (Nabih and Metri, 1971).

PCP breaks down rapidly after application in rice fields. The rate
of decomposition is influenced by sunlight, temperature and soil.
When the sodium salt in dilute aqueous solution was irradiated by
sunlight, two crystalline colored acidic compounds and several minor
substances were produced. One compound was identified as chloranilic
acid (I). A second yellow compound was identified as 3,4,5-trichloro-6-
(2'-hydroxy-3',4',5',6-tetrachlorophenoxy)-o-benzoquinone (II) (Kuwahara
et al., 1966a).

Another minor product (0.10% yield) was identified as tetrachlororesorcinol
(III). Compound IV found in 0.16% yield was characterized and identified
as 2,5-dichloro-3-hydroxy-6-pentachlorophenoxy-p-benzoquinone. Compound
V (0.08% yield) was characterized and identified as 2,6-dichloro-3-
hydroxy-5-(2',4',5',6'-tetrachloro-3'-hydroxyphenoxy)-p-benzoquinone
(Kuwahara, 1966b).

An acidic yellow C_{18}-compound (VI) was also separated from the reaction
mixture. This was identified as 3,5-dichloro-4-(2,3,5,6-tetrachloro-
4-hydroxyphenoxy)-6-(2,3,4,5-tetrachloro-6-hydroxyphenoxy)-o-benzoquinone
(Kuwahara et al., 1966c).

A bacterial isolate, related to the saprophytic coryneform bacteria, was able to metabolize pentachlorophenol as a sole source of carbon and energy. PCP was rapidly metabolized to CO_2 (Chu and Kirsch, 1972).

In cultures of Trichoderma virgatum, pentachlorophenol was methylated to form pentachloroanisole (PCA). Similarly, PCA was formed from PCP by Penicillium sp. and Cephaloascus fragrans (Cserjesi and Johnson, 1972).

Photolysis of sodium pentachlorophenate under different sources of artificial sunlight as well as natural sunlight resulted in only trace amounts of octachlorodibenzo-p-dioxin (Stehl et al., 1971). Irradiation of PCP in hexane gave rise to 2,3,5,6-tetrachlorophenol only (Sloan,1961).

In other studies, PCP was applied to rice fields. Within a few weeks after its application, microorganisms reductively dechlorinated PCP. Products found and identified were 2,3,4,5-, 2,3,5,6- and 2,3,4,6-tetrachlorophenol, 2,4,5- and 2,3,5-trichlorophenol, 3,4- and 3,5-dichlorophenol, and 3-chlorophenol (Ide et al., 1972).

Chloranilic Acid (I)

(II)

(III)

(IV)

PCP

(V)

(VI)
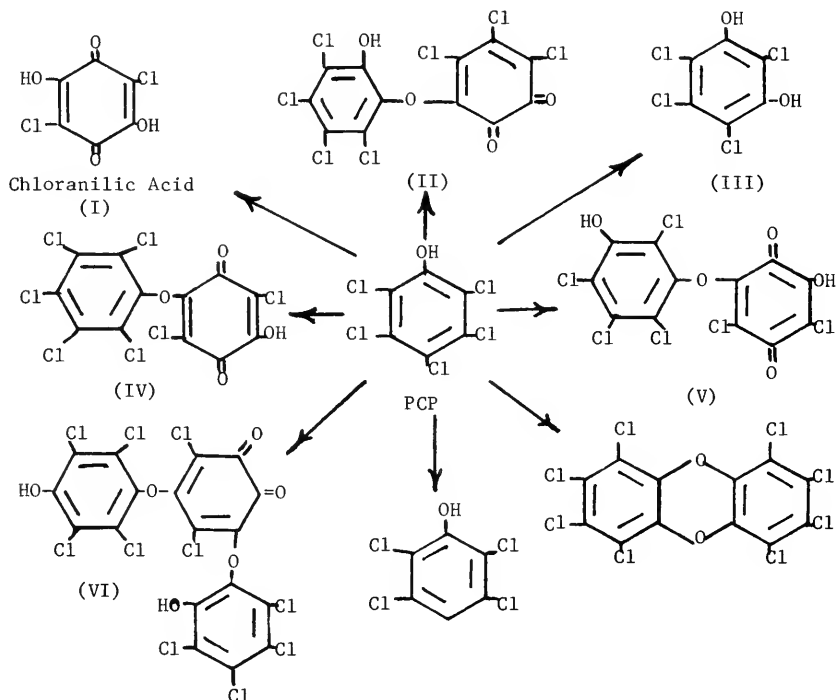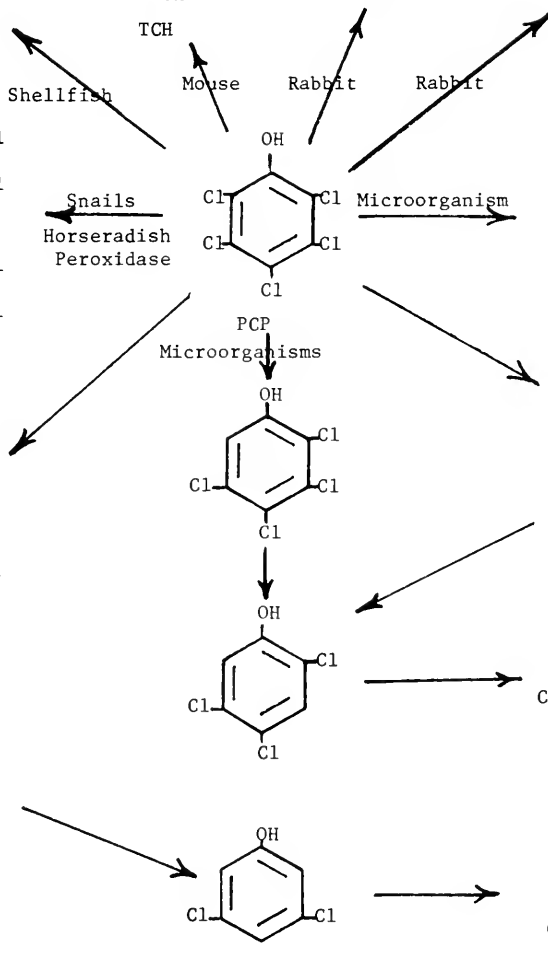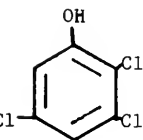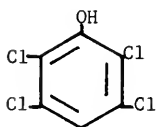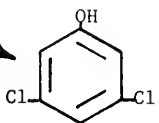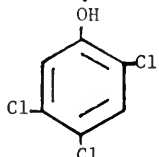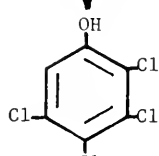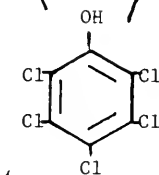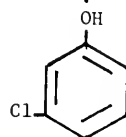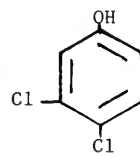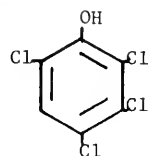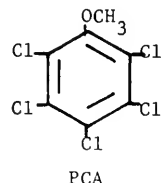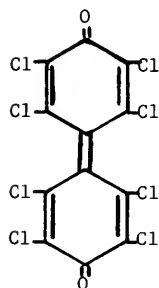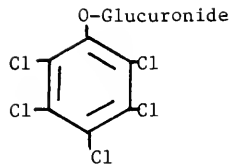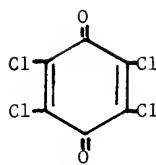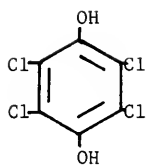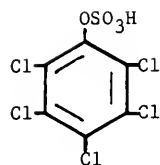
PHENMEDIPHAM [N-(3-m-Tolycarbamoyloxy)phenyl methylcarbamate]

EP-475   [N-(3-Phenylcarbamoyloxy)phenyl ethylcarbamate]

When administered to white rats, phenmedipham and EP-475 were
rapidly metabolized and excreted. Hydrolysis yielded methyl
N-(3-hydroxyphenyl) carbamate (MHPC) and ethyl N-(3-hydroxyphenyl)
carbamate (EHPC), respectively. The hydroxyphenylcarbamates
formed were then degraded to m-aminophenol which was acetylated
to produce 3 -hydroxyacetanilide. These metabolites were then
conjugated as glucuronides and sulfates. All were found in the
urine. Other more polar, but unidentified compounds, were also
present. Both herbicides were also degraded by microsomal and
soluble fractions from rat liver homogenates and blood plasma
from chickens, cow, rat and humans. In vitro the major metabolites
were MHPC and EHPC. Formation of these metabolites was inhibited
by DFP and carbaryl (Sonawane and Knowles, 1971b).

In slightly acid soil, Betanal was decomposed and a half-life of
28-55 days was observed. In other studies, ^{14}C-phenmedipham
(the active component of Betanal) was incubated in an alkaline
soil. In addition to unreacted phenmediphan, methyl-N-(3-
hydroxyphenyl) carbamate (MHPC), m-aminophenol, and an unidentified
compound were recovered (Sonawane and Knowles, 1971a).
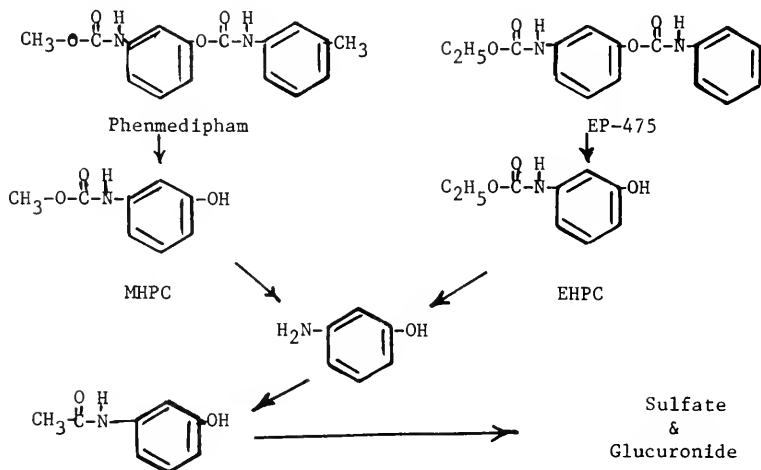
In soil, a half-life of 28-55 days was recorded for phenmedipham (Kossmann, 1970).

After treatment of sugar beet plants with labeled EP-475, the majority of the radioactive material was recovered in chloroform rinses of leaves. When this material was subjected to TLC, unchanged EPTC decreased to 27.1% at 90 days posttreatment. The major metabolite, ethyl N-(3-hydroxyphenyl)carbamate (EHPC), increased to 49.4% in the same time. Some m-aminophenol and 3'-hydroxyacetanilide were also detected (Knowles and Sonawane, 1972).

PHOSDRIN [Methyl 3-dimethylphosphate crotonate]

The bimolecular rate constant for the inhibition of bovine erythrocyte cholinesterase was determined at 37°C to be $1.36 \times 10^5 M^{-1} min^{-1}$ (Braid and Nix, 1969).

PHOSPHAMIDON [N,N-Diethyl 2-chloro-3-dimethylphosphate crotonamide]

In technical preparations of phosphamidon, γ-chlorophosphamidon
is present at a level of one to two percent of the total product.
This compound inhibits bovine ChE about 10 times and human ChE
about 20 times more than pure phosphamidon. However, degradation
of the γ-chloro compound was much greater than that of phosphamidon
when incubated with liver homogenates of mice, dogs, rats, chickens,
rabbits and guinea pigs (Rose and Voss, 1971).

		Micrograms of Compound Degraded by One Gram Liver in Ten Minutes	
Species	Sex	Phosphamidon	γ-Chlorophosphamidon
Mice	♀	66 + 1	1690 + 32
Dogs	♂ & ♀	75 + 7	1114 + 123
Rats	♂	121 + 10	1544 + 162
Rats	♀	95 + 2	1702 + 178
Chickens	♀	122 + 10	280 + 66
Rabbits	♀	130 + 14	1914 + 48
Guinea pigs	♂	180 + 26	1800 + 52

Rats received ^{32}P- and/or ^{14}C-labeled phosphamidon by stomach tube.
Urine analyses indicated the presence of ten radioactive compounds.
In addition to unmetabolized phosphamidon(I), chromatography and
hydrolysis rates indicated the presence of des-N-ethyl phosphamidon(II),
vinyl hydroxyphosphamidon(III), vinyl hydroxy des-N-ethyl phosphamidon(IV),
phosphamidon amide(V), N-hydroxyethyl phosphamidon(VI), N-hydroxyethyl
des-N-ethyl phosphamidon(VII), vinyl hydroxyphosphamidon amide(VIII),
and two compounds containing only the carbon label but not further
identified. Rat and rabbit liver homogenates metabolized phosphamidon
but most products were not organoextractable and not further investi-
gated. Compounds II and V were found in small quantities but the
hydroxy compounds were not detected (Lucier and Menzer, 1971).

The bimolecular rate constant for the inhibition of bovine ethrocyte
cholinesterase was determined at 37°C to be 6.30 x 10^2M^{-1} min^{-1}
(Braid and Nix, 1969).

Structure (I):

$$CH_3O-P(=O)(-OCH_3)-O-C(CH_3)=C(Cl)-C(=O)-N(CH_2-CH_3)(CH_2-CH_3)$$

(I)

Structure (VI):

$CH_3O, CH_3O-P(=O)-O-C(Cl)=C(CH_3)-C(=O)-N(CH(OH)-CH_3)(CH_2-CH_3)$

(VI)

Structure (III):

$CH_3O, CH_3O-P(=O)-O-C(CH_3)=C(OH)-C(=O)-N(CH_2-CH_3)(CH_2-CH_3)$

(III)

Structure (II):

$CH_3O, CH_3O-P(=O)-O-C(Cl)=C(CH_3)-C(=O)-N(H)(CH_2-CH_3)$

(II)

Structure (IV):

$CH_3O, CH_3O-P(=O)-O-C(CH_3)=C(OH)-C(=O)-N(H)(CH_2-CH_3)$

(IV)

Structure (VII):

$CH_3O, CH_3O-P(=O)-O-C(Cl)=C(CH_3)-C(=O)-N(H)(CH(OH)-CH_3)$

(VII)

Structure (V):

$CH_3O, CH_3O-P(=O)-O-C(Cl)=C(CH_3)-C(=O)-NH_2$

(V)

Structure (VIII):

$CH_3O, CH_3O-P(=O)-O-C(CH_3)=C(OH)-C(=O)-NH_2$

(VIII)

293
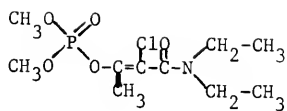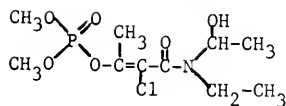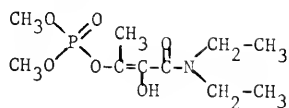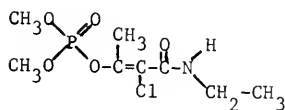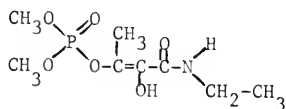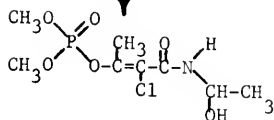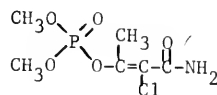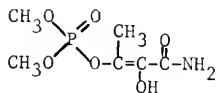
PHOSVEL (Abar, velsicol VCS-506) [O-(2,5-Dichloro-4-bromophenyl)-
O-methyl phenylphosphonothionate]

After application of phosvel to fields of forage corn, the oxygen
analog and the phenol were found. In less than a week after application
to Bermudagrass, 50% of the parent material had disappeared(Leuck
et al., 1969 and 1970).

PHOXIM (Bayer 77488, Valexon, Baythion) [O,O-Diethyl phenylglyoxylo-
        nitrile oxime phosphorothioate]

Phoxim was applied as an emulsifiable concentrate to coastal
bermudagrass and corn. Twenty-one days post-treatment, phoxim
was not detectable in either forage. The oxygen analog of
phoxim was detected on the day of treatment only (Bowman and
Leuck, 1971).

After oral treatment of white mice with ^{32}P-phoxim, four metabolites
were recovered: diethyl phosphoric acid; phoxim carboxylic acid;
O,O-diethyl phosphorothioic acid; and either desethyl phoxim or the
oxygen analog. The large amounts of diethyl phosphoric acid found
in the mouse urine indicated that phoxim was desulfurated to PO-
phoxim which must be hydrolyzed rapidly.

In resistant flies, no carboxylic acid derivative was formed. Some
diethyl phosphorothioic acid was formed. The main metabolic path-
way was via PO-phoxim. Hydrolysis of the latter gave rise to diethyl
and monoethyl phosphate and inorganic phosphate (Vinopal and Fukuto,
1971).

PHTHALATES

Dibutyl and diethyl phthalates, after oral administration to rats, were excreted in urine primarily as their respective monoesters. Some free acid was also formed. The monoesters exhibited greater toxicity than the initial compounds, the diesters (Chambon et al., 1971).

PICLORAM [4-Amino-3,5,6-trichloropicolinic acid]

Picloram was converted to several compounds, one of which was probably a conjugated compound, by the weeds Diplotaxis tenuifolia L. and Prosopis ruscifolia Gris. (Maroder and Prego, 1971).

When incubated with fertile garden soils, picloram persisted for more than 275 days under aerobic and anaerobic conditions (Naik et al., 1972).

<u>PLANAVIN</u> [4-(Methylsulfonyl)-2,6-dinitro-<u>N</u>,<u>N</u>-dipropylaniline]

In fresh rumen fluid, planavin decomposed rapidly with production of three metabolites thought to be the 2,6-diamino-sulfonyl and sulfoxyl analogs and 4-thiomethyl-2,6-diamino-<u>N</u>,<u>N</u>-dipropylaniline (Gutenmann and Lisk, 1970).
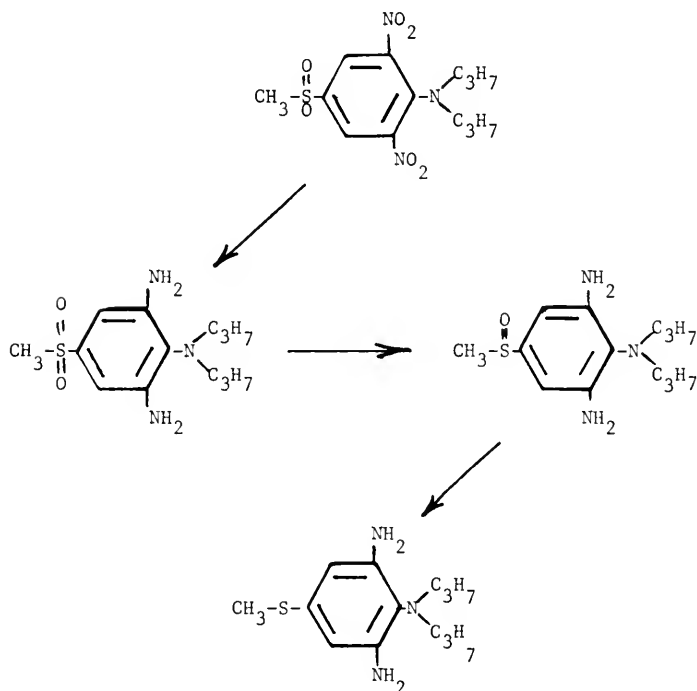
<u>Primicarb</u> [<u>N</u>-Dimethyl-2-dimethylamino-5,6-dimethyl pyrimidine-
          4-carbamate]

Seven hours after treatment of lettuce with primicarb, the parent
compound diminished from the initial 3 - 4 mg/kg to 0.08 - 0.10 mg/kg.
Similarly, residues on cucumbers diminished from 0.2 - 0.3 mg.kg
to about 0.01 mg/kg in 4 hours (Mestres and Espinoza, 1971).

<u>PROPACHLOR</u> [2-Chloro-<u>N</u>-Isopropylacetanilide]

During the first 6 to 24 hours, the metabolism of propachlor was
similar in corn seedlings and in excised leaves of corn, sorghum,
sugarcane, and barley. Propachlor was rapidly metabolized to
water-soluble products by all tissues examined. Two compounds
were identified as glutathion and glutamylcysteine conjugates
of propachlor (Lamoureux et al., 1971).

Very little $^{14}CO_2$ was produced from carbonyl-labeled propachlor
treated soil or pure culture solutions. Dehalogenation was apparently
the major degradative mechanism by <u>Fusarium</u> <u>oxysporum</u> Schlecht. The
major metabolite was 2-hydroxy <u>N</u>-isopropylacetanilide (Kaufman et al.,
1971).

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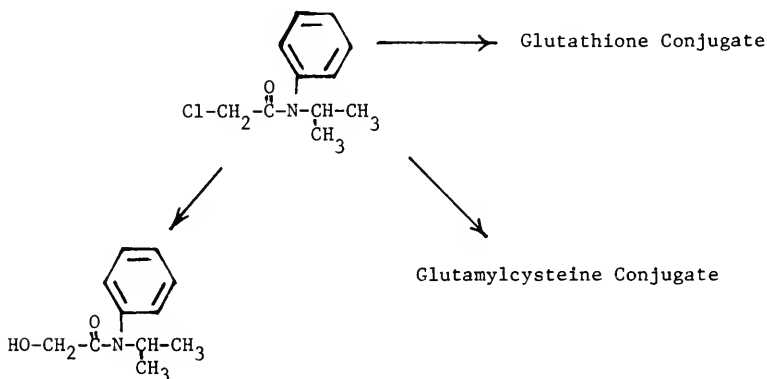
PROPANIL [3',4'-Dichloropropionanilide]

(See also Anilines)

An aryl acylamidase isolated from tulip bulbs was capable of
hydrolyzing propanil. Tests with the enzyme indicated a lack of
sensitive sulfhydryl groups and a pH optimum between 6.8 and 7.8.
The apparent K_m was 2.50×10^{-3}M. From an Arrhenius plot, the
activation energy for hydrolysis of propanil was calculated to be
10.3 k cal/mole (Hoagland and Graf, 1971 and 1972).

Temperature and day length quantitatively modified the ability of
rice (Oryza sativa L.) to metabolize propanil to 3,4-dichloroaniline
(3,4-DCA) and N-3,4-(dichlorophenyl)glucosylamine (Hodgson, 1971).

Propanil was hydrolyzed to its corresponding aniline and alkyl moieties
by soil microbes. Further degradation liberated CO_2 and chloride.
Uniformly ^{14}C-ring-labeled propanil was degraded by soil microorganisms
during three weeks of incubation. About 20-40% of the label was
converted to aromatics such as 3,4-dichloroaniline, 3,3',4,4'-
tetrachloroazobenzene (TCAB) and other highly colored products.
Microbial metabolism also produced compounds identified as 3,3',
4,4'-tetrachloroazoxybenzene, the unsymmetrical 1,3-bis(3,4-dichlorophenyl)-
triazene and 4-(3,4-dichloroanilino)-3,3',4'-trichloroazobenzene
(Chisaka and Kearney, 1970; Kaufman et al, 1971: Kearney et al., 1969
and 1970; Linke, 1970; Linke and Bartha, 1970; Plimmer et al., 1970a
and 1970c. As the concentration of 3,4-dichloroaniline increased
logarithmically, the recovery and formation of TCAB increased;
3,4-dichloroformylanilide and two isomeric forms of TCAB were also
isolated from soil (Kearney and Plimmer, 1972).

A number of microorganisms capable of metabolizing propanil have been
isolated from soil and identified. A strain of Fusarium solani
metabolized propanil primarily to 3,4-DCA (Bartha et al., 1969;
Lanzilotta and Pramer, 1970a and 1970b). Arthrobacter spp. and
Nocardia spp. released 3,4-DCA and formed TCAB (Burge, 1972).
Synergistic interaction of Penicillium piscarium and Geotrichum
candidum brought about formation of TCAB after amide cleavage
(Bordeleau and Bartha, 1971).

Other studies indicated that most 3,4-dichloroaniline existed in
soil as a humus-chloroaniline complex (Bartha, 1971).

Photolysis of dilute aqueous solutions of propanil using $\lambda >$ 310 millimicrons resulted in hydrolysis of the amide, substitution of ring chlorines by hydrogen and hydroxyl groups with subsequent polymerization of the hydroxylated ring (Crosby and Moianen, 1971). In the presence of FMN, sunlight photolysis of propanil yielded 3,4-dichloroaniline which was converted to several compounds. One of these was identified as 3,3',4,4'-tetrachloroazobenzene. A second compound was tentatively identified as 4-(3,4-dichloroanilino)-3,3',4'-trichloroazobenzene (Rosen and Winnett,1969).

After exposure of dilute aqueous solutions of propanil to sunlight, photodecomposition products identified were: 3'-hydroxy-4'-chloro-propionanilide; 3'-chloro-4'-hydroxypropionanilide; 3',4'-dihydroxy-propionanilide; 3'-chloropropionanilide; 4'-chloropropionanilide; propionanilide; 3,4-dichloroaniline; 3-chloroaniline; propionic acid; propionamide; 3,3',4,4'-tetrachloroazobenzene; and a humic acid (Moilanen and Crosby, 1972).

<u>PROPHAM</u> (UC-10854, IPC, Isopropyl carbanilate) [Isopropyl
        N-phenylcarbamate]

Leghorn hens were given a single dose of isopropyl or ring
labeled propham (I). Between 79 and 87% of the label was excreted
via urine and 6-7% via feces. Urinary metabolites were: isopropyl
<u>N</u>-(4-phenylglucuronide)carbamate(II); <u>p</u>-aminophenyl sulfate (III);
isopropyl <u>N</u>-(3-methoxy-4-phenylsulfate)carbamate (IV);isopropyl
<u>N</u>-(4-phenylsulfate)carbamate (V); isopropyl <u>N</u>-(4-hydroxy-3-
phenylsulfate)carbamate (VI); another unidentified conjugate of
compound VI; isopropyl <u>N</u>-(3-phenylsulfate)carbamate (VII); and
isopropyl <u>N</u>-(4-hydroxyphenyl)carbamate (VIII). In the feces, the
metabolites found were compounds II, V, VI and VII. Another
metabolite was characterized only as a hydroxy methoxy substituted
isopropyl carbanilate (Paulson et al., 1971 and 1972a).

Single oral doses of labeled propham were given to eats and a goat.
Urine was collected for six hours after dosing. Labeled metabolites
were separated and then characterized and identified by derivatization,
IR, NMR and mass spectrometry. Structures were confirmed by
synthesis. Goat urinary metabolites included: compound V and its
glucuronide; a conjugate of isopropyl <u>N</u>-(3,4-dihydroxyphenyl)-
carbamate; isopropyl <u>N</u>-(2-hydroxyphenyl sulfate)carbamate (IX);
conjugates of 4-hydroxyaniline; 2-hydroxyaniline; and several
other minor unidentified metabolites. Rat urinary metabolites
included : compounds II and V; <u>p</u>-hydroxyacetanilide sulfate; and
several other minor unidentified metabolites (Paulson et al., 1972b).

After oral or intraperitoneal administration of propham to rats, 80%
of the ^{14}C-isopropyl label appeared in the urine within 4 days.
Smaller amounts appeared in the feces and respired air. About 80% of
the label in the urine was in the form of the sulfate ester of
isopropyl <u>N</u>-(4-hydroxyphenyl)carbamate. This study indicated
formation of little or none of the 2-hydroxy analog (Bend et al.,
1971). Previous studies had indicated formation of <u>N</u>-(2-hydroxy-

PROPOSED RELATIONSHIPS

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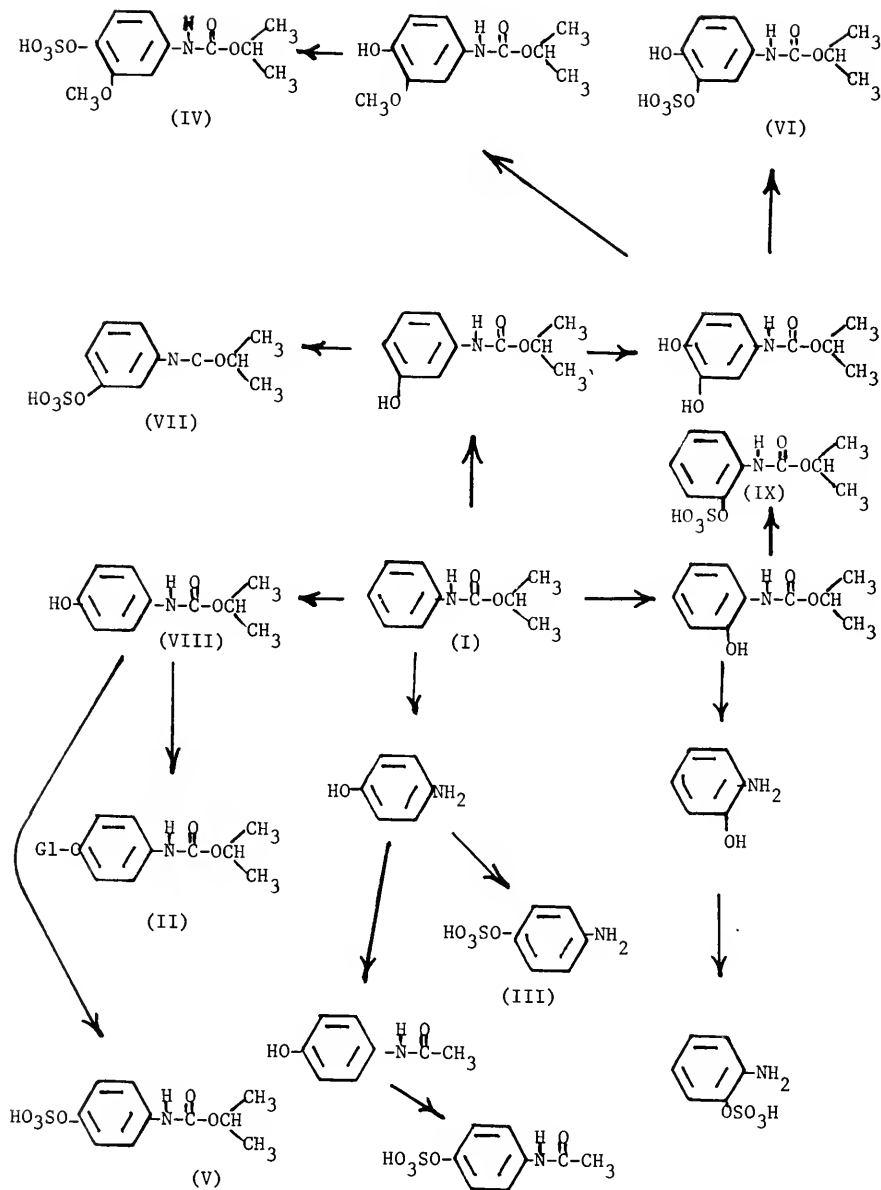
phenyl)carbamate in rats (Holder and Ryan, 1968).

Chlorpropham and propham were not degraded in sterile soil.
Addition of sodium azide to non-sterile soil almost doubled the
persistence of both herbicides. Microorganisms which were capable
of utilizing IPC were isolated from soil and chacterized as
members of the genus Arthrobacter and Achromobacter. Both organisms
metabolized IPC via the aniline (Clark and Wright, 1970a,b).

When sugar beets were treated with propham, propham was oxidized and
hydroxylated. These materials were present as glycosides. After
hydrolysis of the glycosides, N-hydroxypropham and p-hydroxypropham
were identified by chromatography. Some propham was also incorporated
into lignin (Schutte et al., 1971).

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PROPOXUR (Baygon, Bayer 39007) [N-Methyl o-isopropoxyphenylcarbamate]

The metabolism of propoxur by susceptible and resistant larvae
of Culex pipiens fatigans and mouse liver preparations was
studied. More than ten organo-soluble metabolites were observed.
Acetone(V), N-hydroxymethyl propoxur(II) and N-demethyl propoxur(III)
were identified. Another behaved chromatographically similar to
the 5-hydroxy analog(VI). Many of the metabolites were cleaved
when the water layer was incubated with hydrolases (Shrivastava
et al., 1970).

In houseflies (Musca domestica L.) hydrolysis of propoxur was
not important. The major metabolites were primarily hydroxylation
products or degradation products of these compounds. After
incubation of the fly or feces extracts with β-glucuronidase,
aryl sulfatase, and acid phosphatase, the conjugates were
hydrolyzed and liberated each of the hydroxylated carbamates.
The 5-hydroxy propoxur predominated. Compounds II, III, V and
VI were formed by houseflies exposed to propoxur (Shrivastava
et al., 1969). Acetone was also produced by house flies after
injection of labeled propoxur (Casida et al., 1968).

304
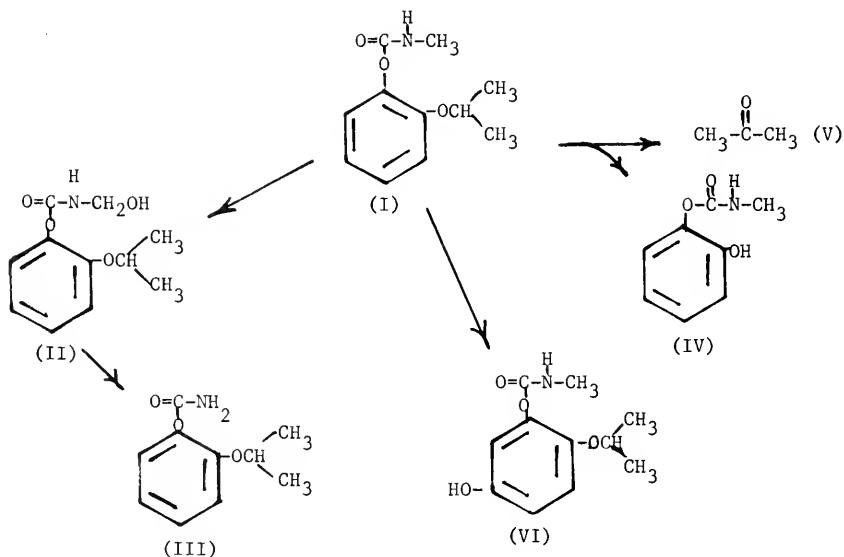
PYRAZON (Pyramin) [5-Amino-4-chloro-3-oxo-2-phenyl-(2H)-pyridazine]

Thin layer chromatography of soil extracts containing labeled pyrazon showed that pyrazon was dephenylated. In sandy loam soil, less than 10% of the herbicide was degraded to 5-amino-4-chloro-3(2H)-pyridazinone (ACP) after 10 weeks at $21^{\circ}C$ (Smith and Meggitt, 1970). In other sutides, loss of pyrazon from soil was exponential and characteristic of the activity of soil microorganisms (Frank and Switzer, 1969a).

When sugar beets (Beta vulgaris L.) were grown in soil treated with pyrazon, the presence of one metabolite in the soil and three in the beets was revealed by TLC. The metabolite in soil was identified as ACP. In the plant, the metabolites were identified as N-glucosyl pyrazon, ACP, and an ACP-complex not further identified (Stephenson and Ries, 1969). In lambsquarters (Chenopodium album L.), pyrazon was accumulated in the leaves but metabolized by the roots. Roots, petioles, and leaf blades of beets rapidly metabolized pyrazon (Frank and Switzer, 1969b).

Irradiation of an aqueous solution of pyrazon through corex filter for 6 hours resulted in a mixture of at least ten products. Two have been identified as 5-amino-4'-chloro-2,2'-diphenyl-4,5-iminodi-3(2H)-pyradazinone and 2,5,7,10-tetrahydro-2,7-diphenylpyrazino (2,3-d;5,6-d')dipyridazine-1,6-dione (Rosen and Siewierski, 1971).

Pyrazon was metabolized in red beet (Beta vulgaris L. cv. Detroit Dark Red) to the N-glucosyl derivative. In 8 susceptible plant species examined, there was no metabolism of pyrazon (Stephenson et al., 1971).

A Gram-negative coccus requiring vitamin B_{12} was found capable of metabolizing pyrazon. The benzene moiety of pyrazon seemed to be used as a carbon source. Several unknowns were detected but disappeared and a residue of 5-amino-4-chloro-pyridazin-3(2H)-one remained (Engvild and Jensen, 1969). Soil microorganisms also were capable of removing the phenyl group (Drescher and Burger, 1970).

Allethrin   [3-Allyl-2-methyl-4-oxocyclopent-2-enyl chrysanthemate]

Dimethrin   [2,4-Dimethylbenzyl chrysanthemate]

Phthalthrin   [3,4,5,6-Tetrahydrophthalimidomethyl chrysanthemate]

Pyrethrin I   [3-Penta-2,4-dienyl-2-methyl-4-oxocyclopent-2-enyl chrysanthemate]

Pyrethrin II [3-Penta-2,4-dienyl-2-methyl-4-oxocyclopent-2-enyl 2,2-dimethyl-3-(1-(methyl 2-methylprop-1-enate))cyclopropanecarboxylate]

Proparthrin   [2-Methyl-5-(2-propynyl)-3-furanylmethyl chrysanthemate]

Resmethrin   [5-Benzyl-3-furylmethyl chrysanthemate]

<u>Allethrin</u> [3-Allyl-2-methyl-4-oxocyclopent-2-enyl chrysanthemate]

After administration of labeled allethrin to male rats, the major
metabolites found were the alcohol-acids (Metabolites E & F).   From
nmr and mass spectra a third metabolite (G) was identified as allethrin
with one cyclopropane methyl hydroxylated and oxidation of the trans-
methyl to a carboxyl group.   Hydrolysis produced small amounts of
allethrolone and chrysanthemum dicarboxylic acid (Casida et al., 1971;
Elliott et al., 1972).

When heated at 150°C, α-DL-trans allethrin gave allethrolone (H),
trans-chrysanthemic acid(I) and 2-allyl-3-methylcyclopent-2-ene-1,4-
dione(J).   A mixture of the 8 isomers of allethrin also gave cis-
chrysanthemic acid(K), pyrocin(L) and <u>cis</u>-dihydrochrysanthemo-δ-
lactone(M).   <u>Cis</u>-allethrin gave product M in addition to products
H, I and J (Baba and Ohno, 1972).

Acid- and alcohol-labeled allethrin was incubated with enzyme systems
from housefly abdomen homogenates.   Each of the ten or more observed
metabolites was an ester, was more polar than allethrin, and was
formed by the mixed-function oxidase system.   The major allethrin
metabolite was $\underline{O}$-demethyl allethrin II (allethrin-ω_t-oic acid).   For
some of the other metabolites observed, structures were proposed as
shown in tentative metabolic pathway.   Similar results were obtained
with <u>in vivo</u> studies (Yamamoto et al., 1969).

A number of streptomyces, bacteria and fungi were capable of hydroxy-
lating cinerone(I) to cinerolone(II).   Upon further incubation, cin-
erolone disappeared.   Two other compounds were isolated and identified
as 2-<u>n</u>-butyl-4-hydroxy-3-methylcyclopenten-1-one(III) and 2-(2^1-<u>cis</u>-
butenyl-4^1-hydroxy)-3-methyl-2-cyclopenten-1-one(IV).   Several yeasts,
some other fungi and streptomyces were also able to metabolize cin-
erone but the products were different from cinerolone (Tabenkin et al.,
1969).

Incubation of allethrone with a strain of <u>Aspergillus niger</u> yielded
three monohydroxylated isomers of allethrolone (LeMahieu et al., 1970).

Allethrin decomposed readily when subjected to irradiation of sun-
light or sun lamp to yield 11 to 15 products.   Photochemical changes
occured in the acid moiety and involved step-wise oxidation of the
trans-methyl group to the alcohol, aldehyde and carboxyl derivatives
and oxidation of the double bond to a keto function with subsequent
rupture to form trans-caronic acid esters.   Other attacks effected
at least six additional changes of the acid moiety.   The alcohol
moiety underwent photochemical alterations also; but the reactions
involved were not known (Chen and Casida, 1969).

	R	R'
Allethrin	CH_3	$CH_2-CH=CH_2$
Allethrin Metabolite E	COOH	$CH_2-CH-CH_2OH$ with OH
F	COOH	$CH-CH=CH_2$ with OH
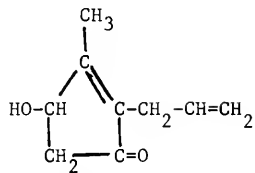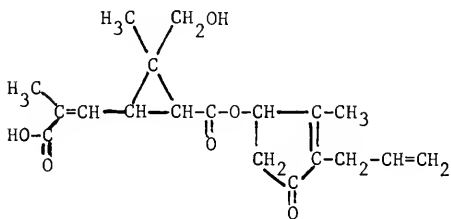
Allethrin Metabolite G

Allethrolone (H)
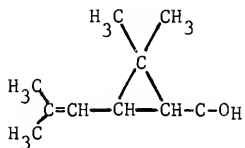
Chrysanthemic Acid
trans= Compound I
cis = Compound K
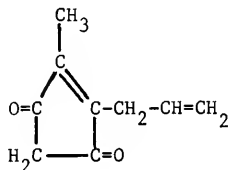
Compound J
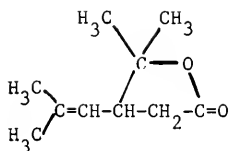
Pyocin (L)
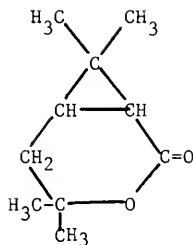
Compound M

	R	R'
Allethrin Metabolite N (Allethrin ω-ol)	CH_2OH	$CH_2-CH=CH_2$
P (Allethrin ω-al)	CHO	$CH_2-CH=CH_2$
R (Allethrin ω-oic acid)	COOH	$CH_2-CH=CH_2$

Allethrin

Metabolite E

Rat | Fly

Metabolite N   Metabolite R —Rat→ Metabolite F

Rat | Fly   Rat

Metabolite P   Fly—Rat   Metabolite G

                    Rat

Allethrolone(H) Chrysanthemic Acid(I)

Allethrone   Allethrolone

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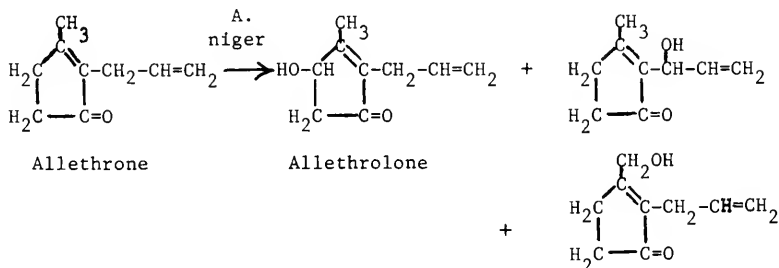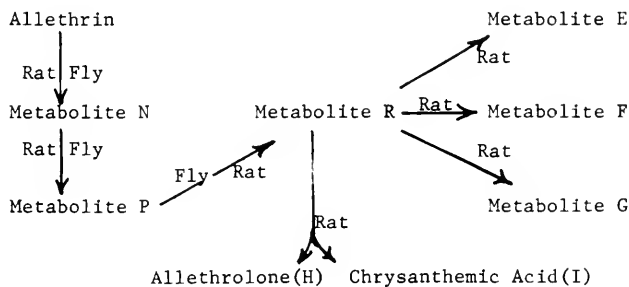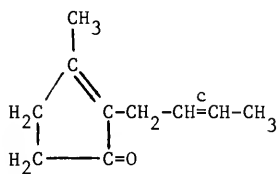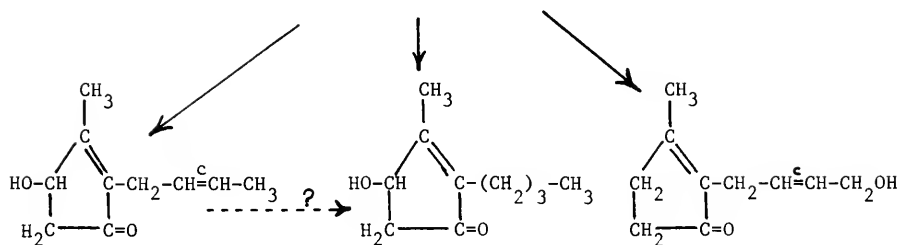
Cinerone (I)

Cinerolone (II)

<u>Dimethrin</u> [2,4-Dimethylbenzyl chrysanthemate]

<u>Phthalthrin</u> (Tetramethrin) [3,4,5,6-Tetrahydrophthalimidomethyl chry-
            santhemate]

<u>In</u> <u>vivo</u> and <u>in</u> <u>vitro</u> studies with houseflies and abdomen homogenate
systems gave rise to the same metabolites. Dimethrin and phthalthrin
were oxidized primarily at the trans-methyl group of the chrysanthemumic
acid moiety to their respectively corresponding carboxyl analogs (Yamamoto
et al., 1969).

Dimethrin and phthalthrin decomposed readily when subjected to irradiation
of sunlight or sun lamp to yield 11 to 15 products. Photochemical changes
occurred in the acid moiety and involved step-wise oxidation of the
trans-methyl group to the alcohol, aldehyde and carboxyl derivatives and
oxidation of the double bond to a keto function with subsequent rupture
to form <u>trans</u>-caronic acid esters. Other attacks effected at least six
additional changes of the acid moiety. The alcohol moiety underwent
photochemical alterations also; but the reactions involved were not known
(Chen and Casida, 1969).

<u>Proparthrin</u> [2-Methyl-5-(2-propynyl)-3-furanylmethyl <u>dl</u>-<u>trans</u>-
            chrysanthemate]

After oral administration of proparthrin to rats, the glucuronide
of 3-hydroxymethyl-2-methyl- 5-(2-propynyl)furan was found and
identified in urine and bile (Nakanishi et al., 1971). Decomposition
also occurs in sunlight (Nakanishi et al., 1970).

Pyrethrin I [3-Penta-2,4-dienyl-2-methyl-4-oxocyclopent-2-enyl chry-
           santhemate]

Pyrethrin II [3-Penta-2,4-dienyl-2-methyl-4-oxocyclopent-2-enyl 2,2-
            dimethyl-3-(1-(methyl 2-methylprop-1-enate))-cyclopropane-
            carboxylate]

Labeled and unlabeled pyrethrins in dimethyl sulfoxide were administered
to male rats by stomach tube. The principal metabolite excreted in
urine has the structure A. Another metabolite was identified as
compound B. Both metabolites were formed in rats from pyrethrin I and '
II. A third metabolite (C) formed from both pyrethrins was a conjugate
of metabolite A. A fourth metabolite (D) was identified as the des-
methyl Pyrethrin II. Pyrethrolone and chrysanthemum dicarboxylic
acid were found in very small amounts only (Casida et al., 1971a,b;
Elliott et al., 1972).

In vivo and in vitro studies with houseflies and abdomen homogenate
systems gave rise to the same metabolites. Pyrethrin was oxidized
primarily at the trans-methyl group of the chrysanthemumic acid moiety
to their respectively corresponding carboxyl analogs (Yamamoto et al.,
1969). Pyrethrin I decomposed readily when subjected to irradiation
of sunlight or sun lamp to yield 11 to 15 products. Photochemical
changes occured in the acid moiety and involved step-wise oxidation
of the trans-methyl group to the alcohol, aldehyde and carboxyl
derivatives and oxidation of the double bond to a keto function with
subsequent rupture to form trans-caronic acid esters. Other attacks
effected at least six additional changes of the acid moiety. The alco-
hol moiety underwent photochemical alterations also; but the reactions
involved were not known (Chen and Casida, 1969).

Photolysis of trans-chrysanthemumic acid caused isomerization to
the cis-isomer. Fragmentation of the cyclopropane ring gave rise to
the olefin, 3,3-dimethacrylic acid (Bullivant and Pattenden, 1971).

		R	R'
Pyrethrin I		CH_3	$CH_2-CH=CH-CH=CH_2$
Pyrethrin II		$\overset{}{\underset{O}{C}}OCH_3$	$CH_2-CH=CH-CH=CH_2$
Pyrethrin Metabolite	A	COOH	$CH_2-CH=CH-\underset{OH}{CH}-CH_2OH$
	B	COOH	$CH_2-\underset{OH}{CH}-CH=CH-CH_2OH$
	C	COOH	$CH_2-CH=CH-\underset{O-Conjugate}{CH}-CH_2OH$
	D	COOH	$CH_2-CH=CH-CH=CH_2$
	E	CH_2OH	$CH_2-CH=CH-CH=CH_2$
	F	CHO	$CH_2-CH=CH-CH=CH_2$

Pyrethrin I   PyrethrinII

Rat | Fly   Rat

↓

Metabolite E

Rat | Fly

↓

Metabolite F   ⟶   Metabolite D

              Rat | Rat

Metabolite B ⟵   Metabolite A

                            | Rat

                         Metabolite C

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Resmethrin [5-Benzyl-3-furylmethyl dl-trans-chrysanthemate]
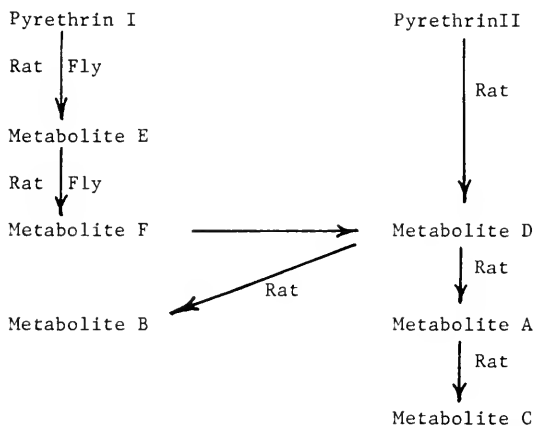
[14]C-Furan-ring-labeled resmethrin was orally administered to Sprague-
Dawley rats. Absorption and distribution of ^{14}C to the tissues was rapid.
Only a small amount of unchanged resmethrin was found in the tissues.
After three weeks, elimination of all radioactivity was complete.
Urine contained 36%; feces, 64%. After separation of the urinary
metabolites, identification indicated that 5-benzyl-3-furancarboxylic
acid, free (IV) and as the glucuronide (V), was the main metabolite.
Hydroxylation and oxidation of the acid yielded the α-hydroxy (VI)
and benzoyl (VII) analogs, the 4-hydroxyfuran (VIII) and 4-hydroxy-
benzyl (IX) derivatives. The flucuronide and the sulfate of compound
(IX) were also observed. Some unidentified conjugates of (IV) con-
tained phosphorus. In bile, traces were found of the parent alcohol
(II), formed by hydrolysis of resmethrin (Miyamoto et al., 1971).

R=Chrysanthemate
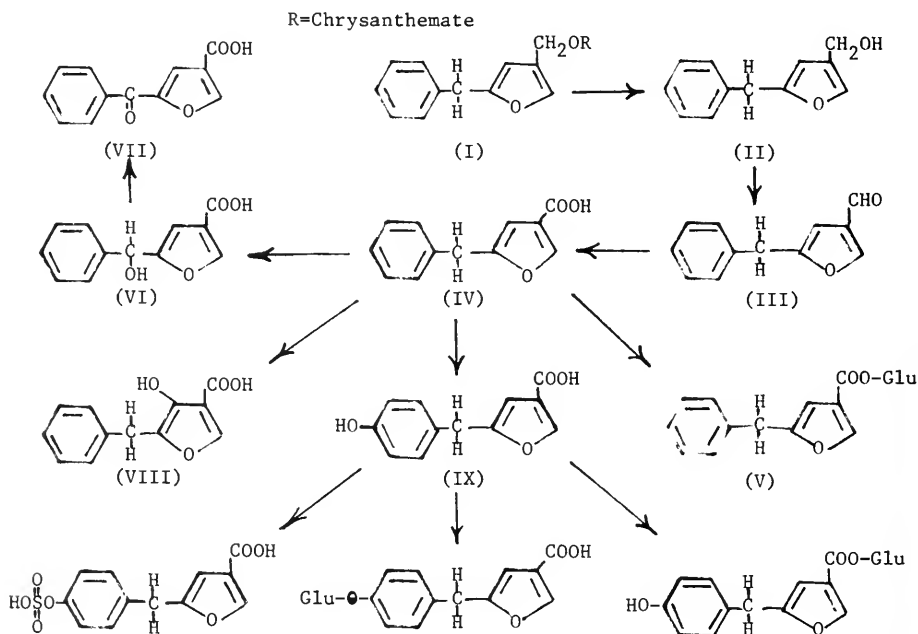
ROBENDINE [1,3-Bis(p-chlorobenzylideneamino) guanidine hydrochloride]

After oral administration of labeled Robendine(I) to chickens, the radioactivity was rapidly excreted. Up to 80% of the excreted label was as unchanged Robendine. A number of metabolites retained the p-chlorobenzylidene-C^{14} label. Mass spectrometry suggested that they were mixed conjugates of ornithine and lysine containing p-chlorobenzoic acid. In some tissues, a metabolite found was identified as compound II (Zulalian et al., 1970a).

Robendine was also fed to rats. Two urinary metabolites were identified as p-chlorohippuric acid(IV) and p-chlorobenzoic acid(III) (Zulalian et al., 1970b).

(II)

(III)

(IV)
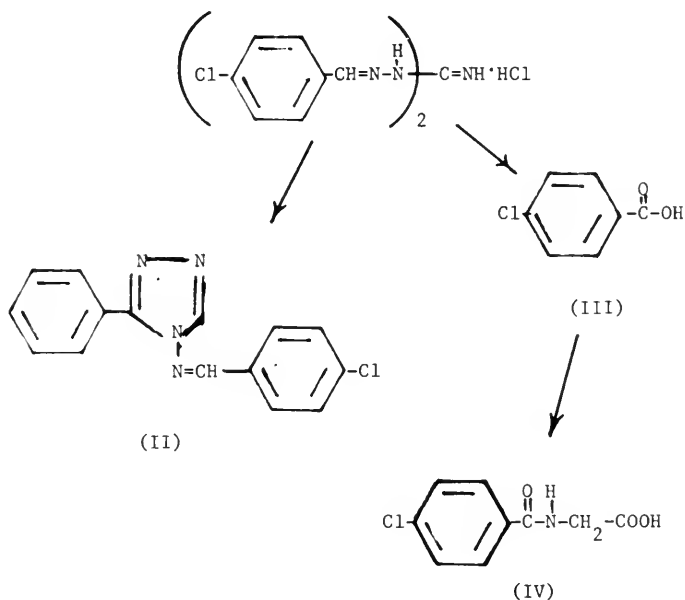
When ^{14}C-labeled ronidazole was administered to turkeys in their diets, more than 80% of the dose was excreted and 1-2% was exhaled as ^{14}CO$_2$. 2-Hydroxymethyl-1-methyl-5-nitroimidazole was found in trace amounts. N-methylglycolamide, methylamine and oxalic acid were also identified as metabolites. Extensive biodegradation of ronidazole and recombination into normal body metabolites produced labeled protein, nucleic acid and lipid fractions in whole liver and in glutamic acid, aspartic acid and citric acid cycle intermediates (Rosenblum et al., 1972).
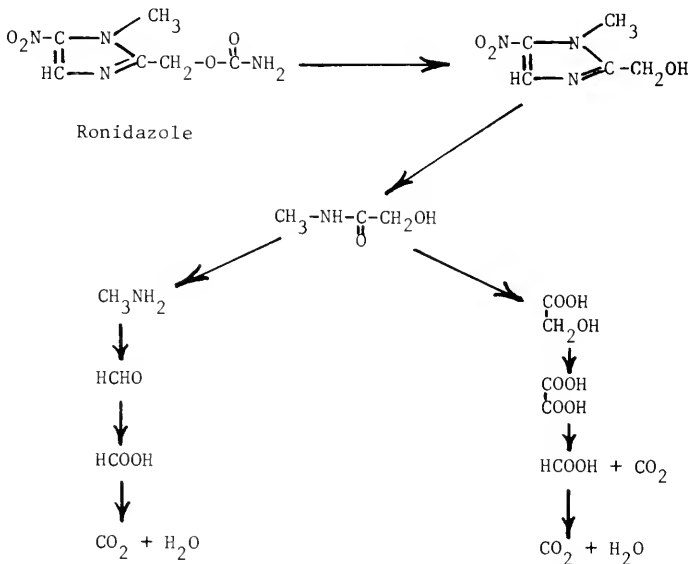
Rotenone, incubated with the microsome mixed function oxidase system of mammalian liver, fish liver and insect tissues, was metabolized to 8^1-hydroxyrotenone (C), dihydrodihydroxyrotenone (F), Rotenolone I (A) and II (B), hydroxyrotenolone I (D) and dihydrodihydroxy-rotenolone I (G). The pathways seem to be the same in these test species for detoxification of rotenone. However, the results of in vitro and in vivo studies indicated that the selective toxicity of rotenone was related to the effects of components in the soluble fraction of the homogenates. The soluble fraction of the liver homogenates enhances metabolism of rotenone whereas the soluble fraction of cockroach fat body and mid-gut homogenates inhibits the metabolism of rotenone. Inhibition resulted from the presence of a protein with a molecular weight of 6,000 to 15,000 (Fukami et al., 1969).

Methanolic solutions of rotenone exposed to UV light gave rise to at least 10 products and photolysis was 80% complete in two hours. Products identified were: 6aβ, 12aβ-rotenolone; tubaic acid; 6^1, 7^1-epoxyrotenone; O-demethylrotenone; 6aβ, 12aα-rotenolone; 6aα, 12aβ-rotenolone; 6aα, 12aα-rotenolone; rotenonone; rissic acid; 4,5-dimethoxysalicylic acid; and CO_2 (Cheng et al., 1971).

Rotenone was also exposed to sunlight on plant leaves and sun-light, UV or sunlamp on glass surfaces. The photodecomposition of rotenone is summarized in a figure (Cheng et al., 1972).

Rotenone and its derivatives: conversion scheme showing Rotenone at the center converting to 8'-Hydroxyrotenone (C), 6',7'-dihydro-6',7'-dihydroxyrotenone (F), Rotenolone I (A), Rotenolone II (B), 8'-Hydroxyrotenolone I (D), 8'-Hydroxyrotenolone II (E), 6',7'-dihydro-6',7'-dihydroxyrotenolone I (G), and 6',7'-dihydro-6'7'-dihydroxyrotenolone II (H).
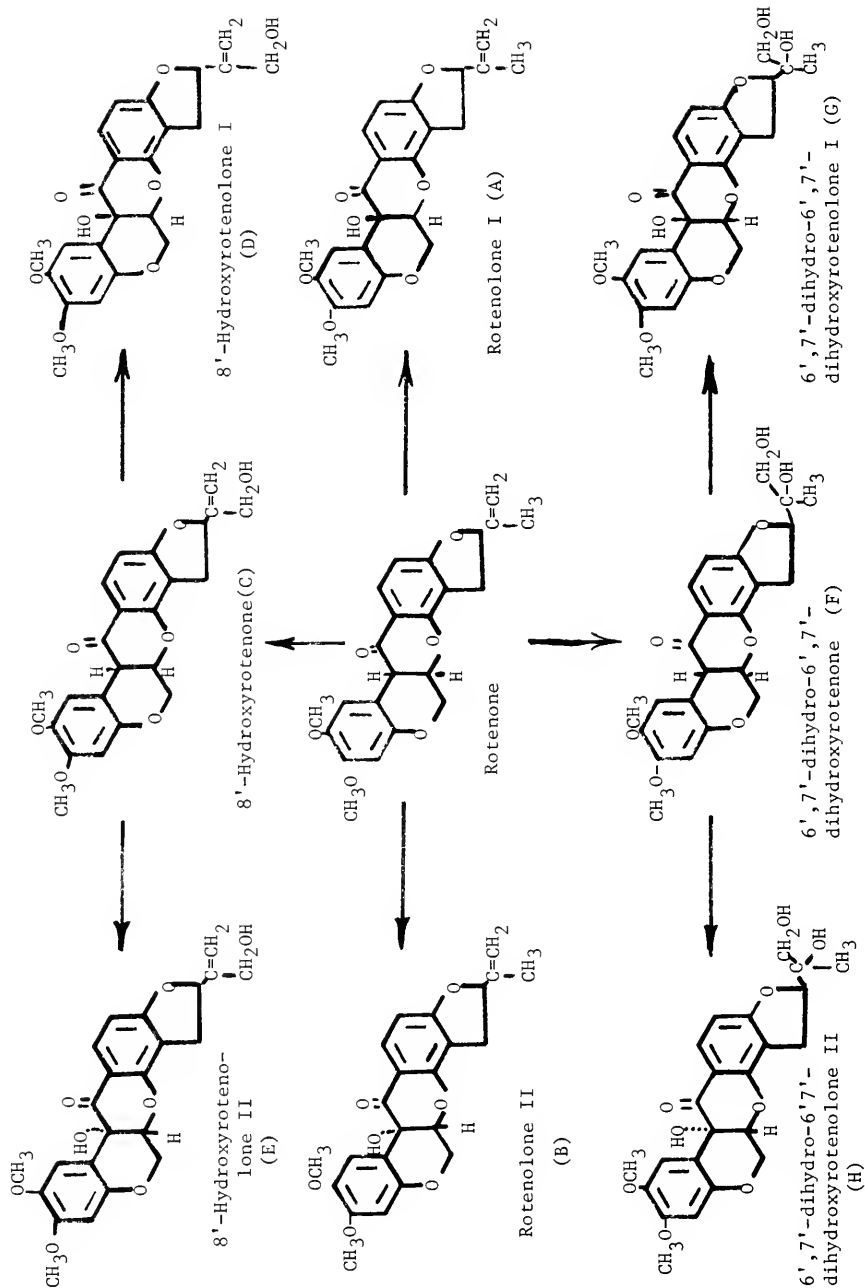
Photodecomposition products formed by irradiation of rotenone in methanol and benzene (1) or formed when rotenone was exposed to light as deposits on glass surfaces or on bean leaves (2).

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<u>SAN - 6706</u> [4-Chloro-5-dimethylamino-2-(3-trifluoromethylphenyl)-
          3(2H)-pyridazinone
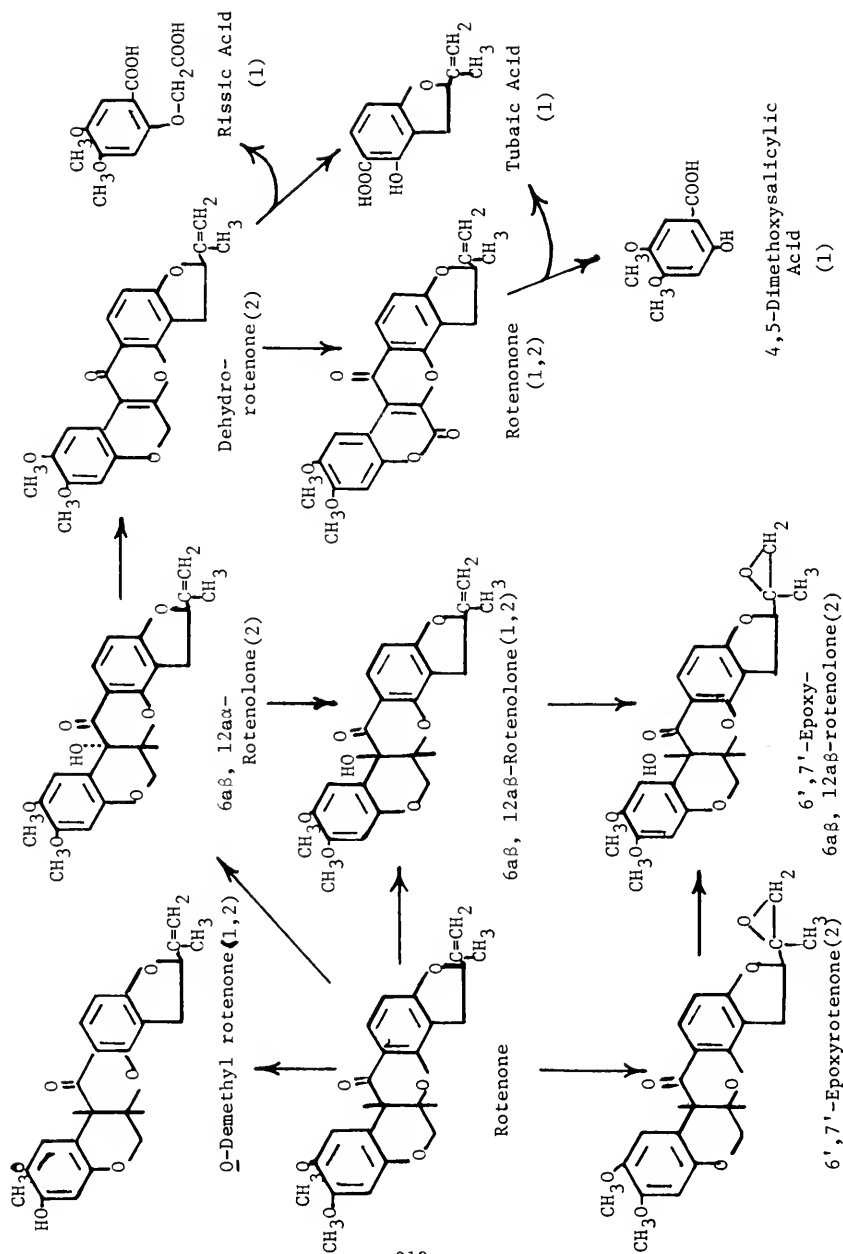
Cranberry plants (<u>Vaccinium</u> <u>macrocarpon</u> Ait.) were allowed to
absorb San-6706-^{14}C via the roots. Chromatographs of root
extracts from plants treated for 8 days indicated the presence
of two compounds. In addition to the original material, the
monodemethylated analog was detected. After the root medium
was allowed to stand for 14 days with tagged San-6706, ten
spots were detected on the autoradiographs. Two were identified
as the original material and the monodemethylated analog (Devlin and
Yaklich, 1972).
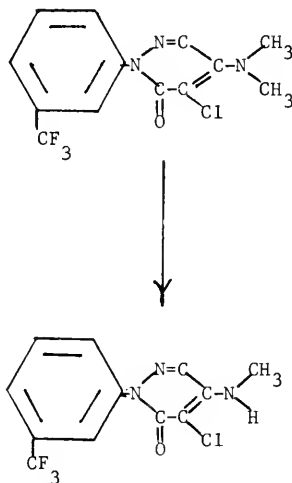
<u>SOLAN</u> [3'-dichloro-4'-methyl-<u>p</u>-valerotoluidide]

Solan was microbially hydrolyzed to its corresponding aniline and alkyl moieties. Further degradation liberated CO_2 and Cl^-. Microbial metabolism also produced 3,3',4,4'-tetrachloroazobenzene and 3,3',4,4'-tetrachloroazoxybenzene from 3,4-dichloroaniline. Several transformations of the amino group occurred and included acetylation, formylation, and oxidation. Hydroxylation of the aniline ring also occurred (Kaufman et al., 1971).

<u>SOMAN</u>   [Pinacolyl methylphosphonofluoridate]

Wheat, grown in hydroponic culture, was treated with Soman via
the culture solution. In the plants, grown for 24 hours in the
presence of Soman and then transferred to clean solution for
24 hours, no Soman was found; but much pinacolyl hydrogen
methylphosphonate and low concentrations of another compound,
probably hydrogen methylphosphonofluoridate were found. After
five weeks in clean solution, methylphosphonate was also observed.
In the absence of plants, Soman half-life in the hydroponic culture
solution was about 2-2 1/2 days (about 20% in 24 hours); in the
presence of wheat plants, $t_{1/2} \simeq 5$ hours (Hambrook et al., 1971).

STAUFFER R-3828 [S-(p-Chloro-α-phenylbenzyl) O,O-diethyl phosphorodithioate]

Cattle were fed this compound at rate of 5 or 10 mg/kg/day for eight weeks. At the end of this period, residue levels were 109 and 302 ppm, respectively. Residues were not completely eliminated 14 weeks after cessation of feeding of this chemical. Residues of the parent compound were found mainly in the fat. Residues of the oxygen analog were found in fat only. These residues, about 2% that of R-3828 during the feeding period, rapidly decreased to zero when feeding ceased (Claborn et al., 1970).

STAUFFER R-16661   [2-[Methoxy(methylthio)phosphinylimino]-3-
                    ethyl-5-methyl-1,3-oxazolidine]

In the cotton plant, R-16661 was slowly metabolized. A small
amount of the 4-keto analog and a trace of what was thought
to be the 4-hydroxy analog were found.

In the housefly, the 4-keto analog was found but the 4-hydroxy
compound was not detected. In vitro studies with housefly and
mosquito larvae homogenates gave metabolite patterns similar to
those seen in living houseflies (Fukuto et al., 1972).
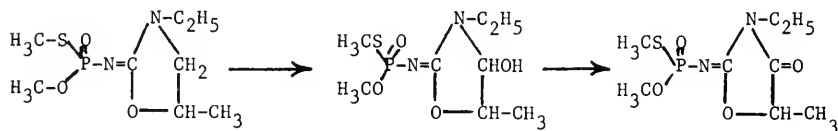
SUPRACIDE (GS-13005) [$\underline{S}$-(2-methoxy-5-oxo-Δ^2-1,3,4-thiadiazolin-4-yl) methyl $\underline{O},\underline{O}$-dimethyl phosphorodithioate]

Balance studies with labeled Supracide in rats were conducted. There was rapid excretion of metabolites via urine and expired air. The product of final oxidation and the main metabolite (up to 36% of the applied dose) was determined to be CO_2. Two other metabolites in the urine were 2-methoxy-4-methylsulfinylmethyl-Δ^2-1,3,4-thiadiazolin-5-one (25%) and the corresponding sulfone (7%). The methylthiomethyl derivative did not appear in significant amounts (Dupuis et al., 1971).

Supracide was incubated in 10,000xg supernatant of rat liver homogenate. After hydrolytic cleavage, the carbonyl group was liberated spontaneously in the form of CO_2. In the presence of $^{14}CH_3$-L-methionine, the methylsulfinylmethyl and methylsulfonylmethyl metabolites were formed (Dupuis et al., 1971).

In milk of a goat, about 1% of the administered label was found within 72 hrs. after a single oral dose. About 95% of this was in the form of polar materials and no Supracide or the oxon analog were found (Dupuis et al., 1971).

For ten weeks, ruminating bull calves received supracide by capsule once daily at rates up to 2.0 mg/kg of live weight. At 2.0 mg/kg, three of five animals succumbed at the 12th, 33rd and 34th days. Tissue analyses did not show the presence of the Supracide oxygen analog. The parent compound was present at low levels (<0.05 ppm) at the 2.0 mg/kg dose level but not at 1.0 mg/kg (Polan et al., 1969a).

When labeled supracide was administered to a lactating cow, analysis of milk, urine, and feces indicated that extensive degradation of the material had occurred. No supracide or its oxygen analog was found in the milk. The highest level of radioactivity found was 0.11 ppm in the liver (Cassidy et al., 1969a). In rumen of cows, degradation of supracide was apparently due to microbial activity. Degradation to water-soluble metabolites was linear (Polan et al., 1969b).

The locust $\underline{L}$. migratoria degraded the thiadiazole ring. Some CO_2 and unidentified water-soluble metabolites were formed (Dupuis et al., 1971).

After exposure of bean plants and alfalfa to supracide, the oxon and 2-methoxy-Δ^2-1,3,4-thiadiazolin-5-one were observed in addition to CO_2 and unidentified polar material. Another compound observed was thought to be a conjugate of desmethyl supracide. Similar observations were made with other field grown agricultural crops (Cassidy et al., 1969b; Dupuis et al., 1971; Eberle and Hormann, 1971; Mattson et al., 1969).

In soil, supracide was rapidly degraded. With the exception of the conjugate, the same compounds were observed in soil as in plants (Dupuis et al., 1971; Eberle and Hormann, 1971).

In lactating cows, supracide was rapidly degraded. The principal routes of elimination were CO_2 and urine. Supracide was readily absorbed from the rumen. Milk contained the sulfone and sulfoxide (Polan and Chandler, 1971).
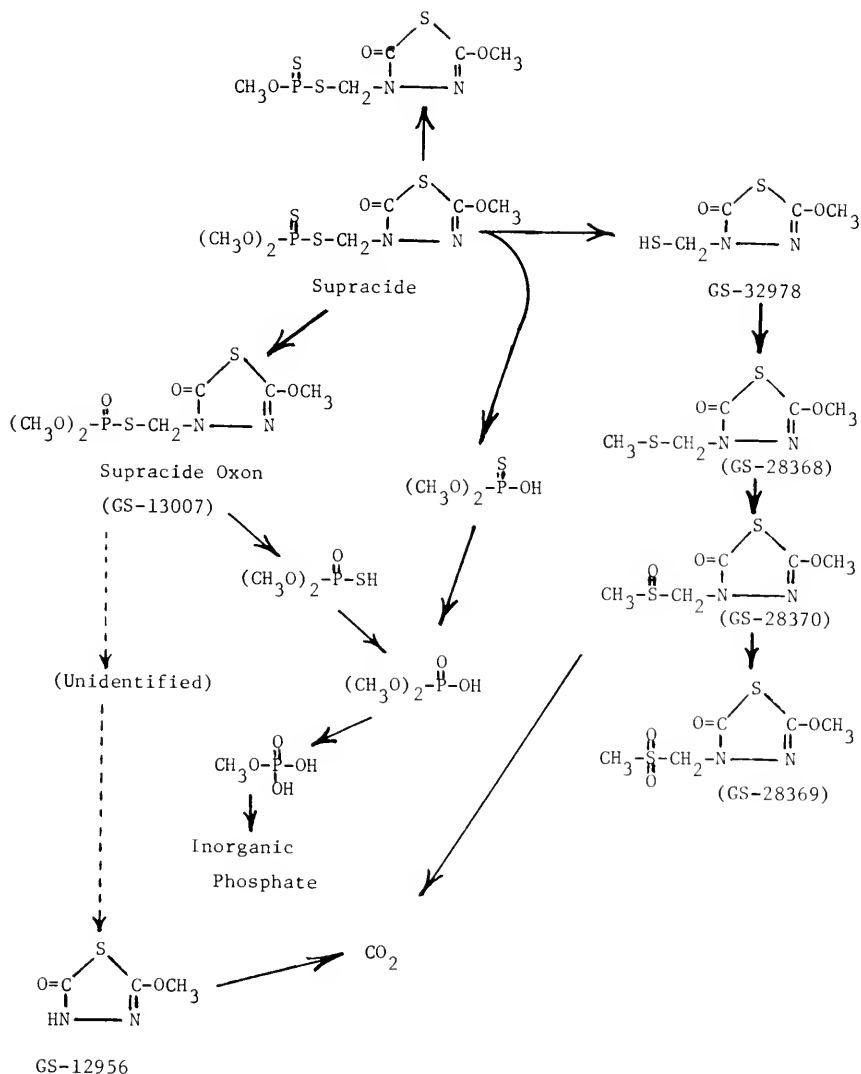
<u>SWEP</u> [Methyl-<u>N</u>-(3,4-dichlorophenyl)carbamate]

Swep was incubated at 28°C with freshly collected Nixon sandy loam (pH 5.5). After 40 days, some Swep remained intact; but thin-layer chromatography indicated that a portion of the herbicide was transformed to a variety of products. Two of these have been isolated and identified as dichloroaniline (DCA) and tetrachloroazo-benzene (TCAB) (Bartha and Pramer, 1969).

<u>2,3,6-TBA</u> [2,3,6-Trichlorobenzoic acid]

In the presence of lake water and sodium benzoate, 2,3,6-TBA was co-metabolized by the microbial population (Horvath, 1972). <u>Brevibacterium</u> sp. degraded 2,3,6-TBA by a cometabolic process. Oxidation occurred in a bi-model manner with the total uptake of oxygen being 1 μmole oxygen per μmole herbicide. One μmole CO_2 was released per μmole 2,3,6-TBA oxidized. One μmole chloride was also released. TLC provided evidence of formation of 3,5-dichloro-catechol.

Initial oxidation of 2,3,6-TBA occurred without CO_2 formation or chloride cleavage. On the basis of the ability of the enzyme system to metabolize 2,3,6- and 2,4,5-trichlorophenols but not 3,4,5-trichlorophenol, it was proposed that the pathway for 2,3,6-TBA was via oxidation through 2,3,6-trichloro-4-hydroxybenzoate and 2,3,5-trichlorophenol (Horvath, 1971).

An <u>Achromobacter</u> sp., grown on benzoic acid, cometabolized formed 3,5-dichlorocatechol to 2-hydroxymuconic semialdehyde (Horvath et al., 1970).

<u>TCA</u> [Trichloroacetic acid]

A <u>Pseudomonas</u> sp., isolated from soil solutions containing TCA, was incubated with TCA labeled at either C-1 or C-2. In addition to evolution of $^{14}CO_2$, some radioactivity was incorporated into cellular components. Serine and two unidentified metabolites were observed on paper chromatography (Kearney et al., 1969).

TELODRIN [1,3,4,5,6,7,8,8-Octachloro- 1,3,3a,4,7,7a-hexahydro-4,7-
         methanoisobenzofuran]

Telodrin was transformed, after intravenous injection into rats,
to a hydrophylic metabolite which was hydrolyzed to the lactone
(Kaul et al., 1970).

In rats, tetramisole(I) was rapidly degraded. More than 50
metabolites were observed in the urine within a few hours of
administration. A major metabolite was identified as p-(2,3-
dihydroimidazo[2,1-b]thiazol-6-yl)phenol S-oxide(II). A minor
metabolite related to compound II was identified as the dioxide III
(Zulalian et al., 1969).

Oxidation of the ring system by rats yielded neutral and acidic
metabolites. From collected urine, several compounds were isolated
and identified: 4-phenyl-2-thioxo-1-imidazolidineacetic acid(IV); 2-
oxo-4-phenyl-1-imidazolidineacetic acid (V); and 4-phenyl-2-imidazo-
lidinone(VI) (Champagne et al., 1969). Conjugates of identified
compounds were also present. p-Hydroxytetramisole was found in
urine as a conjugate only. When the free form was fed to rats,
only the conjugate of p-hydroxytetramisole was found, indicating
that this compound does not serve significantly as an intermediate
in the formation of other metabolites (Plaisted et al., 1969).
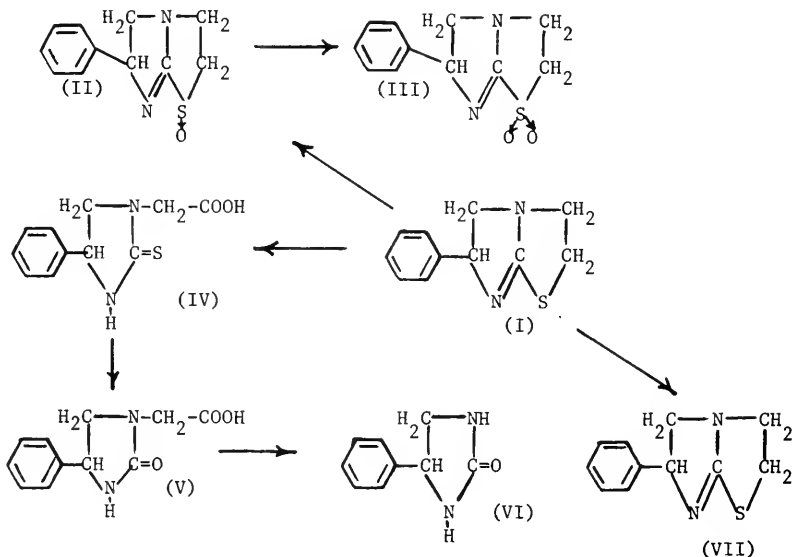
TETRASUL [2,4,4',5-Tetrachlorodiphenylsulfide]

Tetrasul was orally administered to rats for up to two months.
About 40% was absorbed from the G. I. tract. Within one week,
65% of the dose was excreted via feces and 10% via urine.
Accumulation in fat was about 10 times higher than in organs.
Biological half-life was about 4 days in organs and tissues and
equilibrium between intake and excretion was attained in about
14 days. The major routes of metabolism were oxidation of the
sulfide to sulfoxide and sulfone and hydroxylation in the 3'-
position with subsequent breakdown of the molecule on either
side of the sulfur (Verschuuren, 1969).

After ip administration of TFM to male Holtzman rats, analysis of urine indicated that some TFM was reduced to the aminophenol (RTFM). Both TFM and the reduced form were excreted as polar, acid labile compounds. Treatment with β-glucuronidase released both TFM and RTFM, indicating the presence of some glucuronides (Lech, 1971).

In rainbow trout, the major in vivo metabolite of TFM apparently was the glucuronide. This was found in the bile and in the tank during exposure of trout to TFM. In vitro nitro reductase reduced TFM to the aminophenol. The reduced compound was acetylated by liver and kidney extracts. In the presence of UDPGA and TFM, TFM glucuronide was also formed in vitro (Lech, 1972; Lech and Costrini, 1972).

In aqueous solutions, TFM was stable. However, in the presence of lake and river sediments, TFM concentration decreased as a function of time. Addition of KCN & HgCl$_2$ did not significantly affect the rate of disappearance but addition of phenol slowed the rate of decrease. Fluoride analyses indicated that some fluorine of TFM was released as fluoride (Magadanz and Kempe, 1968).

Culture techniques were used to obtain TFM-degrading bacteria from lake and river muds. Although one mixed culture of bacteria was able to degrade the TFM in a solution of 100 ppm within seven days, a pure culture having the characteristics of a Pseudomonas sp. was unable to fully degrade the entire amount of TFM present in the media (Sutton and Kempe, 1970).

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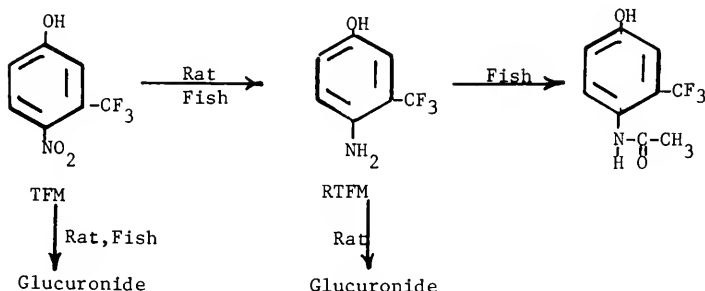
Thiabendazole [2-(4^1-thiazolyl) benzimidazole]

Radioactivity in cotton plants treated with labeled thiabendazole was present in higher weight molecular complexes. Hydrolysis of the complexes did not yield thiabendazole, indicating that the complexes were probably with metabolites (Wang et al., 1971).

<u>THIMET</u> (Phorate) [<u>O</u>,<u>O</u>-Diethyl <u>S</u>-ethylthiomethyl phosphorodithioate]

Coastal bermudagrass (<u>Cynodon</u> <u>dactylon</u> L.) and corn (<u>Zea</u> <u>Mays</u> L.) were treated with an emulsifiable concentrate of phorate at rates up to 2 lbs/acre. In addition to unchanged phorate, the residue on corn contained phorate sulfoxide and sulfone and the sulfoxide and sulfone of the oxygen analog. The oxygen analog itself was not detected. Total residue on corn was less than 1.0 ppm 14 days after treatment for all application rates tested. The same metabolites were observed in bermudagrass. Total residues were less than 1.0 ppm 21 days after treatment (Leuck and Bowman, 1970).

In soil, phorate was oxidized to phorate oxygen analog and the sulfones and sulfoxides of both phorate and the oxygen analog (Getzin and Shanks, 1970).

Thimet was subjected to γ-radiation from ^{60}Co. Decomposition was reduced at lower temperatures; increased with increasing doses of radiation; and was greater in hexane and acetone than in water. The sulfone, oxygen analog sulfone, and oxygen analog sulfoxide were present (Grant et al., 1969).

Thiocyanate

Lethane 384 [2-(2-Butoxyethoxy)ethyl thiocyanate]

Thanite [Isobornyl thiocyanoacetate]

In living mice and houseflies, HCN was released after ingestion of many organothiocyanates. Studies with soluble fractions of mouse liver or fly homogenates, have shown that glutathione S-transferases catalyzed the reaction of glutathione with the thiocyanate sulfur and released HCN. From the mouse liver soluble fraction, four glutathione S-transferases acting on octyl thiocyanate have been resolved by chromatography; from whole housefly homogenate soluble fraction, three were resolved. Lethane 384, several alkyl thiocyanates and benzylthiocyanate reacted in this system. Thanite reacted with glutathione to release hydrogen cyanide even in the absence of glutathione S-transferase (Ohkawa et al., 1971 and 1972).

After injection of labeled thiocyanate into rats, radioactive carbon was exhaled as CO_2 and cyanide. $^{14}CO_2$ was also seen after injection of $^{14}CN^-$ and the studies further indicated that $^{14}CO_2$ appeared as soon as SCN^- was converted to CN^-. The appearance of labeled carbon as ureide carbon was explained on the assumption that the pathway leads from cyanide to formate and thence to compounds involved in one-carbon metabolism. The biological half-life of thiocyanate-C was 3.6 days (Boxer and Rickards, 1952).

Labeled KSCN was incubated with hydrogen peroxide and a lactoperoxidase prepared from raw skim milk. Initial products were cyanide and sulfate. Cyanide was produced but disappeared from the solution on prolonged incubation. The loss of cyanide was due not to volatilization but to oxidation. In the presence of thiocyanate and its oxidation products, cyanide was rapidly destroyed in the lactoperoxidase system. Cyanate, ammonia and carbonate were formed as secondary products of cyanide oxidation. Cyanate was rapidly hydrolyzed at pH 5.7 to ammonia and carbonate. A rise in absorption at 235 mμ was shown to be a thiocyanate-enzyme complex (Chung and Wood, 1970).

A number of enzyme systems have been used to study thiocyanate oxidation. In one system, the oxidation by H_2O_2 was pH independent and no cyanide appeared to be released as an intermediate (Wilson and Harris, 1960 and 1961).

$$4H_2O_2 + SCN^- \rightarrow HSO_4^- + HOCN + 3H_2O$$

$$\downarrow 2H_2O$$

$$NH_4^+ + HCO_3^-$$
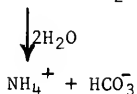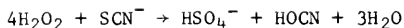
Oxidation of thiocyanate could be expected to produce the unstable intermediate thiocyanogen. No evidence for its formation could be found owever, in an analogous reaction, it was formed by oxidation of thiocyanate by peroxomonosulfate (Smith and Wilson, 1967; Soderback, 1919).

$$2SCN^- + H_2O_2 \rightarrow (SCN)_2 + 2OH^-$$

$$\downarrow H_2O$$

$$HOSCN + HSCN$$

$$H_2SO_4 + HCN + 2HSCN \longleftarrow \Big|$$
$$H_2O$$
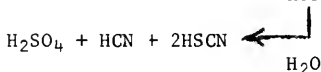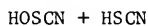
Sulfite, readily oxidized to sulfate, has been proposed as an intermediate but has not been observed (Oram and Reiter, 1966). Sulfur dicyanide has also been proposed as an intermediate; although it has been detected in acid catalyzed oxidation of thiocyanate (Wilson and Harris, 1961), none has been detected in the lactoperoxidase system. The delayed loss of cyanide observed in this system and the production of cyanate could be accounted for by intermediate formation of sulfur dicyanide. The following sequence of reactions has been suggested (Chung and Wood, 1970):

$$H_2O_2 + SCN^- \rightarrow OSCN^- + H_2O$$

$$OSCN^- + H_2O_2 \rightarrow OOSCN^- + H_2O$$

$$H_2O + OOSCN^- \rightarrow HSO_3^- + HCN$$

$$HSO_3^- + H_2O_2 \rightarrow HSO_4^- + H_2O$$

$$\overline{3H_2O_2 + SCN^- \rightarrow HSO_4^- + HCN + 2H_2O}$$

$$HOSCN^- + HCN \rightarrow S(CN)_2 + H_2O$$

slow $\quad S(CN)_2 + H_2O \rightarrow HOCN + HSCN$

rapid $\quad S(CN)_2 + H_2O_2 \rightarrow^* H_2SO_4 + 2HCN$

$$*\text{lactoperoxidase}$$

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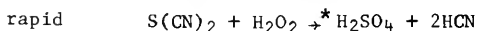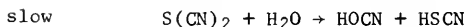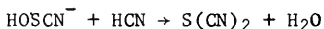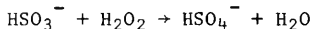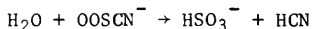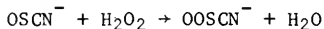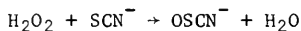
The release of cyanide in vivo results in some resynthesis of thio-
cyanate through thiosulfate and mercaptopyruvate transsulfurase
systems. The carbons of cyanide and thiocyanate were found to be
related to a common pool resulting from the thiocyanate-cyanide
cycle. Sulfur was removed from the thiocyanate pool by oxidation
to sulfate (Lang, 1933; Fiedler and Wood, 1956; Boxer and Richards,
1952).

THIRAM (TMTD, Tetramethyl thiuram disulfide) [Bis(N,N-dimethylthio-
          carbamoyl)disulfide]

Orally administered thiuram was metabolized by warmblooded animals
to tetramethylthiourea, dimethylamine salt of dimethyldithiocarbamate,
carbon disulfide and dimethylamine (Vekstein and Khitsenko, 1971).

<u>TIBA</u> [2,3,5-Triiodobenzoic Acid]

Rats received oral doses of ^{14}C- and ^{125}I-labeled TIBA. Within four days, 72-75% of the radioactivity was excreted in the urine and 24-28% in the feces. Analysis of urine revealed the presence of 2,5-diiodobenzoic acid, free and conjugated; 2-hydroxy-3,5-diiodobenzoic acid; and 3,5-diiodobenzoic acid (Barker et al., 1971).

In laying hens given a single oral dose of TIBA, the biological half-life was 22 hours. In addition to unchanged TIBA, seven metabolites were found: 2,3-diiodobenzoic acid (2,3-DIBA); 2,5-diiodobenzoic acid (2,5 DIBA); 3,5-diiodobenzoic acid (3,5-DIBA); and four unknown materials (Rowles et al., 1970).

After treatment of soybeans with labeled TIBA, 3,5-DIBA and 2,5-DIBA were found in leaves and harvested seeds. Much of the label was not extractable (Spitznagle et al., 1969).

After oral administration of TIBA to a cow, milk was collected at intervals up to 54 hours later. Analyses by chromatography indicated the presence of traces of unresolved monoiodobenzoic acids (MIBA), 2-HO-5-MIBA, 3,5-diiodobenzoic acid (3,5-DIBA), 2-HO-3, 5-DIBA, triiodobenzoic acid (TIBA), and three unidentified metabolites (McGee et al., 1969).

In soil, labeled TIBA was degraded by microorganisms to CO_2. In addition to some unchanged TIBA, three metabolites were recovered. Two were identified as 2,5-DIBA and 3,5-DIBA. The third metabolite was not identified (Moy and Ebert, 1972).

Triethyltin

Studies with alkyl tin compounds have indicated that these compounds disrupt mitochondria oxidative phosphorylation by binding at the site of histidine residues. These studies have also indicated that rat hemoglobin and guinea pig liver bind two molecules of triethyl tin.

Binding Affinity at pH=8.0

Guinea pig liver protein	$2 \times 10^6 M^{-1}$
Rat hemoglobin (1st triethyl tin bound)	$3.5 \times 10^5 M^{-1}$
(2nd " " ")	$5.0 \times 10^5 M^{-1}$
Mitochondria	$4.7 \times 10^5 M^{-1}$

(Aldridge and Rose, 1969; Aldridge and Street, 1970 and 1971; Rose, 1969; Rose and Lock, 1970).

<u>Trimethyltin</u>

The affinity constant of the binding of trimethyltin to site 1 of rat liver mitochondria was about $1.2 \times 10^4 M^{-1}$; to rat hemoglobin, $2.8 \times 10^5 M^{-1}$ (Aldridge and Street, 1970 and 1971). Trimethyltin complexed with histidine residues (Aldridge and Rose, 1969).

Triphenyltin acetate (TPTA)

Aromatic labeled ^{14}C-triphenyltin acetate was added to soil at levels of 5.0 and 10.0 p.p.m. and shielded from light. The half-life was approximately 140 days. A constant linear rate of carbon dioxide evolution occurred up to the 80th day, at which time one-third of the phenyl carbon had been released. The rate then fell to less than half the initial rate. In heat sterilized soil, the rate of CO_2 evolution was insignificant. It was felt, therefore, that TPTA degradation was the result of microbial activity (Barnes et al., 1971).

Triphenyltin chloride

After application to plants, triphenyltin chloride degraded to diphenyltin and monophenyltin compounds (Bock and Freitag, 1972).

<u>TOK</u> [2,4-Dichloro-4'-nitrodiphenyl ether]

Aqueous solutions or suspensions of the herbicide TOK were exposed
to sunlight or simulated sunlight. Photodecomposition was
characterized by rapid cleavage of the ether linkage and formation
of p-nitrophenol and 2,4-dichlorophenol. Other identified products
included 4-chlorocatechol, 4-nitrocatechol, 4-chloro-4'-nitrodiphenyl
ether, 2,4-dichloro-4'-aminodiphenyl ether and p,p'-di-(2,4-dichloro-
phenoxy)azobenzene (Crosby and Nakagawa, 1971).

<u>TORAK</u> (Hercules 14503) [<u>S</u>-(2-Chloro-1-phthalimidoethyl)-<u>O</u>,<u>O</u>-diethyl phosphorodithioate]

Torak was fed to a dairy cow at a level of 5 ppm for 4 days. Neither Torak nor its oxygen analog were found in the milk. Torak was absent from urine but about 3% of the total Torak fed was found in the feces. Diethyl phosphate and diethyl thiophosphate were found in urine. The latter metabolite was also found after incubation of Torak with liver 10,000xg supernate. Torak was not metabolized by rumen fluid (St. John et al., 1971).

On oranges and lemons, the residue half-life of Torak was 40-60 days and 60-80 days. There was no evidence of the presence of the oxygen analog (Westlake et al., 1971).
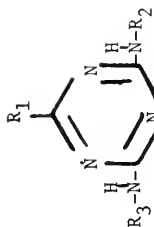
	R_1	R_2	R_3
Atrazine	I. Cl	CH_3-CH_2-	$(CH_3)_2-CH-$
	Ia. Cl-	H-	$(CH_3)_2-CH-$
	Ib. Cl-	CH_3-CH_2-	H
Hydroxyatrazine	II. OH	CH_3-CH_2-	$(CH_3)_2-CH-$
	III. OH	H-	H-
	IV. OH	H-	$(CH_3)_2-CH-$
	V. OH	CH_3-CH_2-	H-
	VI. OH	H-	$HOOC-\overset{OH}{C}H-$
	VII. OH	CH_3-CH_2- (or $HOOC-CH_2-$)	$CH_3-\overset{O}{\underset{}{C}}H-COOH$ (or $(CH_3)_2-CH-$)
	VIII. $S-CH_2-\overset{O}{\underset{}{C}}H-\overset{H}{N}-CH_2-\overset{O}{\underset{}{C}}-OH$ $HN-\overset{O}{\underset{}{C}}-CH_2-CH_2-\overset{C=O}{\underset{OH}{C}}H-NH_2$	CH_3-CH_2-	$(CH_3)_2-CH-$

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	R_1	R_2	R_3
IX.	$S-CH_2-CH(-C=O,OH)-NH-C(=O)-CH_2-CH_2-CH(-C=O,OH)-NH_2$	CH_3-CH_2-	$(CH_3)_2-CH-$
X.	CH_3O-	CH_3-CH_2-	$(CH_3)_2-CH-$
XI.	CH_3-CH_2O-	CH_3-CH_2-	$(CH_3)_2-CH-$
XII.	Cl	CH_3-CH_2-	CH_3-CH_2-
XIII.	OH	CH_3-CH_2-	CH_3-CH_2-
XIV.	OH	$H-$	CH_3-CH_2-
XV.	OH	$H-$	$H-$
XVI.	$S-CH_2-CH(-COOH)-NH-C(=O)-CH(-CH_2-CH_2-CH(-C=O,OH)-NH_2)-N-CH_2-COOH$	CH_3-CH_2-	CH_3-CH_2-
XVII.	$S-CH_2-CH(-COOH)-NH-C(=O)-CH_2-CH_2-CH(-COOH)-NH_2$	CH_3-CH_2-	CH_3-CH_2-
XVIII.	Cl	$(CH_3)_2-CH-$	$(CH_3)_2-CH-$

Simazine (compounds X–XI region)

Propazine (compound XVIII)

		R_1	R_2	R_3
	XIX.	OH	$(CH_3)_2-CH-$	$(CH_3)_2-CH-$
Ametryne	XX.	CH_3S-	CH_3-CH_2-	$(CH_3)_2-CH-$
	XXI.	H	CH_3-CH_2-	$(CH_3)_2-CH-$
Simetryne	XXII.	CH_3S-	CH_3-CH_2-	CH_3-CH_2-
	XXIII.	H	CH_3-CH_2-	CH_3-CH_2-
Prometryne	XXIV.	CH_3S-	$(CH_3)_2-CH-$	$(CH_3)_2-CH-$
	XXV.	OH	$(CH_3)_2-CH-$	$(CH_3)_2-CH-$
	XXVI.	H	$(CH_3)_2-CH-$	$(CH_3)_2-CH-$
GS-14254	XXVII.	CH_3O-	CH_3-CH_2-	$CH_3-CH_2-CH-CH_3$
	XXVIII.	CH_3O-	CH_3-CH_2-	$HOOC-CH_2-CH-CH_3$
	XXIX.	CH_3O-	H-	H-
	XXX.	CH_3O-	H-	$CH_3-CH_2-CH-CH_2OH$
	XXXI.	CH_3O-	H-	$CH_3-CH_2-CH-CH_3$, OH
	XXXII.	CH_3O-	H-	$CH_3-CH_2-CH-CH_3$
	XXXIII.	OH	H-	H-

	R_1	R_2	R_3
XXXIV.	OH	H–	$HOCH_2-CH_2-\overset{\mid}{CH}-CH_3$ or $CH_3-\underset{OH}{\overset{\mid}{CH}}-CH-CH_3$
XXXV.	OH	CH_3-CH_2-	$CH_3-CH_2-\overset{\mid}{CH}-CH_3$
XXXVI.	OH	CH_3-CH_2-	H–
XXXVII.	OH	CH_3-CH_2-	$HOCH_2-\overset{\mid}{CH}-CH-CH_3$
XXXVIII.	CH_3O-	H–	$HOCH_2-CH_2-\overset{\mid}{CH}-CH_3$
XXXIX.	N_3-	CH_3-CH_2-	$(CH_3)_3-C-$
XL.	NH_2-	CH_3-CH_2-	$(CH_3)_3-C-$
XLI.	NH_2-	H–	$(CH_3)_3-C-$
XLII.	N_3-	H–	$(CH_3)_3-C-$
XLIII. (WL 9385)	Cl–	CH_3-CH_2-	$(CH_3)_3-\overset{\mid}{\underset{CN}{C}}-$
XLIV. (Cyanazine)	HO–	CH_3-CH_2-	$(CH_3)_3-\overset{\mid}{\underset{CN}{C}}-$

	R$_1$	R$_2$	R$_3$
XLV.	S-CH$_2$-CH(-C(O)-N(H)-CH$_2$-COOH)-CH$_2$-CH(NH$_2$)-C(=O)OH, HN-C(O)-CH$_2$	H-	(CH$_2$)$_3$-C-CN
XLVI.	S-CH$_2$-CH(-C(O)-N(H)-CH$_2$-COOH)-CH$_2$-CH(NH$_2$)-C(=O)OH, HN-C(O)-CH$_2$	CH$_3$-CH$_2$-	(CH$_2$)$_3$-C-CN
XLVII.	S-CH$_2$-CH(-COOH)-CH$_2$-C(O)-CH$_3$, 2 HN-C(O)-CH$_2$	H-	(CH$_2$)$_3$-C-CN
XLVIII.	S-CH$_2$-CH(-COOH)-CH$_2$-C(O)-CH$_3$, HN-C(O)-CH$_2$	CH$_3$-CH$_2$-	(CH$_2$)$_3$-C-CN
XLIX.	Cl-	H-	(CH$_2$)$_3$-C-CN
L.	Cl-	CH$_3$-CH$_2$-	(CH$_2$)$_3$-C-C(=O)-NH$_2$
LI.	HO-	CH$_3$-CH$_2$-	(CH$_2$)$_3$-C-C(=O)-NH$_2$
LII.	Cl-	H-	(CH$_2$)$_3$-C-C(=O)-NH$_2$

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	R_1	R_2	R_3
LIII.	$Cl-$	CH_3-CH_2-	$(CH_3)_2-\overset{}{C}-COOH$
LIV.	$HO-$	CH_3-CH_2-	$(CH_3)_2-\overset{}{C}-COOH$
LV.	$Cl-$	$H-$	$(CH_3)_2-\overset{}{C}-COOH$
LVI.	$HO-$	$H-$	$(CH_3)_2-\overset{}{C}-COOH$
LVII.	$Cl-$	CH_3-CH_2-	$H-$
LVIII.	N_3-	CH_3S-	$(CH_3)_2-CH-$
LIX.	NH_2-	CH_3S-	$(CH_3)_2-CH-$
LX.	NH_2-	$H-$	$(CH_3)_2-CH-$
LXI.	N_3-	$H-$	$(CH_3)_2-CH-$

	R_1	R_2	R_3
1	CH_3	$C_2H_5^-$	$CH_3-CH-CH_2-CH_3$
2	H	$C_2H_5^-$	$CH_3-CH-CH_2-CH_3$
3	H	H	$CH_3-CH-CH_2-CH_3$
4	H	$C_2H_5^-$	H
5	H	$C_2H_5^-$	$CH_3-CH-CH_2-CH_2OH$
6	CH_3	$C_2H_5^-$	$CH_3-CH-CH_2-COOH$
7	CH_3	H	H
8	CH_3	H	$CH_3-CH-CH_2-CH_2OH$
9	CH_3	H	$HOCH_2-CH-CH_2-CH_3$
10	H	H	H
11	H	H	$CH_3-CH-CH_2-CH_2OH$
12	CH_3	H	$CH_3-CH-CH_2-CH_3$

Rats were given doses of various triazine analogs. Urinary metabolites from ring-labeled 1 separated into 15 components. Of these, compounds 6, 7, 8, 9, 10 were identified. After administration of compound 2, four urinary metabolites were detected. Three were identified as the parent compound, compound 4, and compound 5. The major metabolite of compound 1 was compound 10 (Larson and Bakke, 1971).

AGLYPT (Bayer 79758) [4-amino-3-methylthio-6-phenyl-1,2,4-triazin -5-one]

Aqueous solutions of Aglypt were irradiated by sunlight. Chromatography
of ethyl acetate extracts revealed three spots. Two were due to some
original material and a small amount of an unidentified product. The
third component was identified as 3-methylthio-6-phenyl-1,2,4-triazin -
5-one (Rosen and Siewierski, 1971b).

<u>AMETRYNE</u>   [2-Ethylamino-4-isopropylamino-6-methylthio-<u>s</u>-triazine]

Studies with rats showed that ametryne (XX) was dealkylated following an oral dose (Oliner et al., 1969).

Ultraviolet irradiation (at 253.7 nm.) of ametryne in benzene, water or methyl, ethyl or <u>n</u>-butyl alcohol formed 4-ethylamino-6-isopropyl-amino-<u>s</u>-triazine (XXI) (Pape and Zabik, 1969 and 1970).

<u>ATRAZINE</u> [2-Chloro-4-ethylamino-6-isopropylamino-<u>s</u>-triazine]

Single doses of labeled atrazine (I) and hydroxyatrazine (II) were
administered to rats. The radioactivity was excreted mainly in the
urine. Nineteen urinary metabolites were separated. Four of these
were identified as compounds II, III, IV and V. Two other metabolites
were characterized by mass spectrometry but not identified: tenta-
tively, compounds VI and VII (Bakke et al., 1972).

After incubation of sorghum leaf sections with atrazine, two closely
related metabolites were isolated and identified as <u>S</u>-(4-ethylamino-6-
isopropylamino-2-<u>s</u>-triazino)glutathione (VIII) and γ-L-glutamyl-<u>S</u>-(4-
ethylamino-6-isopropylamino-2-<u>s</u>-triazino)-L-cysteine (IX) (Lamoureux
et al., 1970 and 1972). In other studies, wild cane (<u>Sorghum</u> <u>bicolor</u>
L.) metabolized 70% of the atrazine absorbed and translocated to the
shoot during 24 hours. Hydroxyatrazine (II), compound VI, and water
soluble metabolites which were chromatographically identical to the
peptide conjugates VIII and IX were observed (Thompson, 1972).

When absorbed through the roots of corn plants, atrazine gave rise to
hydroxyatrazine (II) as well as the glutathione analog (VIII). When
introduced directly into leaf tissue, atrazine was metabolized mainly
to compound VIII. Hydroxyatrazine was not metabolized to the glutathione
analog when absorbed from leaf surface (Shimabukuro et al., 1970).

Most corn lines rapidly detoxified atrazine by glutathione conjugation.
Hydroxyatrazine was found only when atrazine was applied via the roots.
In root fed plants, the partially <u>N</u>-dealkylated compound 2-chloro-4-
amino-6-isopropylamino- and 2-chloro-4-amino-6-ethylamino-<u>s</u>-triazines
were also observed (Shimabukuro et al., 1971).

With four related 2-chloro-<u>s</u>-triazines, the glutathione and γ-glutamyl-
cysteine conjugates were formed more rapidly in the excised leaves of
sorghum, corn and sugar cane-resistant species than in the susceptible
species, barley (Lomoureux et al., 1972).

A soluble glutathione <u>S</u>-transferase, obtained from corn leaves,
catalyzed the conjugation of several substituted 2-chloro-<u>s</u>-triazines
with reduced glutathione. One mole of chloride ion was produced for
every mole of glutathione conjugate produced. Apparent K_m values were
3.7×10^{-5} and 2.4×10^{-3}M (Frear and Swanson, 1970).

Cotton treated with atrazine detoxified the herbicide by $\underline{N}$-dealkylation. This occurred in both glanded and non-glanded cotton (Shimabukuro and Swanson, 1970).

Sudangrass (<u>Sorghum</u> <u>sudanese</u>) and sorghum (<u>Sorghum</u> <u>bicolor</u>) metabolized atrazine primarily to 2-chloro-4-amino-6-ethylamino-$\underline{s}$-triazine and 2-chloro-4-amino-6-isopropylamino-$\underline{s}$-triazine. Corn metabolized atrazine to the 2-hydroxy analog (Roeth and Lavy, 1971).

In Hawaiian soils, atrazine was converted primarily to the 2-hydroxy analog (Obien and Green, 1969).

When soil organisms were incubated with atrazine, $^{14}CO_2$ was observed only when the side chains were labeled. Degradation proceeded primarily via $\underline{N}$-dealkylation. Formation of hydroxyatrazine was also observed. These studies were conducted with strains of the following organisms:

Aspergillus	fumigatus
"	ustus
"	flavipes
Rhizopus	stolonifer
Fusarium	moniliforme
"	roseum
"	oxysporum
Penicillum	decumbens
"	janthinellum
"	rugulosum
"	luteum
Trichoderma	viride

(Kaufman and Blake, 1970)

<u>Sertaria</u> <u>Panicum</u> species absorbed and translocated atrazine, and metabolized it to water-soluble derivatives. Hydroxy derivatives were detected. Peptide conjugates were the major metabolites formed by each species or variety (Thompson, 1972).

In other studies, soil microorganisms were incubated with ^{14}C-ring-labeled atrazine and its 2-hydroxy analog. With soil extracts, 1.67% of hydroxyatrazine-^{14}C and 0.005% of atrazine-^{14}C was converted to CO_2. Under anaerobic conditions, no $^{14}CO_2$ evolved (Goswami and Green, 1971).

Degradation of atrazine in soil was dependent on soil type, moisture content and herbicide concentration. Conversion of atrazine to hydroxyatrazine varied from 10-40% in four soils. Hydrolysis predominated in one soil as the pathway for detoxification. In the other

three soils, detoxification proceded via chemical hydrolysis and microbial degradation of the ethyl side chain (Skipper and Volk, 1972).

When irradiated by UV in methanol, atrazine formed the methoxy analog (X). Similarly the ethoxy analog (XI) formed in ethanol solution and the hydroxy (II) analog in water (Pape and Zabik, 1969 and 1970).

Studies with chemical systems, such as Fenton's reagent, which generate hydroxyl radicals, were able to dealkylate $\underline{s}$-triazines such as atrazine (Plimmer et al., 1971). Degradation of atrazine was catalyzed by montmorillonite. The adsorbed hydrolytic degradation product was predominantly in the keto form (Russell et al., 1968).

The rate of degradation of atrazine in soil was determined to follow first order kinetics with no lag period (Zimdahl et al., 1970).

	Rate of degradation per month at		Arrhenius activation energy (kcals/mole)
	13.2 C	31.2 C	
Atrazine	0.19	0.60	10.8
Simazine	0.21	0.55	9.2
Ametryne	0.14	0.26	6.1

This compound (LVIII) when irradiated in methanol at 253.7 or 300 nm, yielded the amine LIX, LX, LXI and some unidentified volatile sulfur compounds. Prolonged irradiation converted the parent compound almost completely to the reduced and dealkylated compound LX. In carbon tetrachloride, only compound LXI was formed when LVIII was irradiated (Pape and Zabik, 1972).

This compound was applied as a water suspension to ten day old
seedlings. The material was transformed within the tissue primarily
into 2-ethylamino-4-S-(β-D-glucopyranosyl)-6-isopropylamino-s-
triazine(C) and 2,4-dihydroxy-6-isopropylamino-s-triazine(A). Traces
of 2-mercapto-4-ethylamino-6-isopropylamino-s-triazine(B), the
corresponding disulfide(E), and the hydroxy derivative(D) were also
found (Mildner et al., 1972).

CYANAZINE (Bladex, Fortrol)   [2-Chloro-4-cyano-1-methylethylamino-
                              6-ethylamino)-s-triazine]
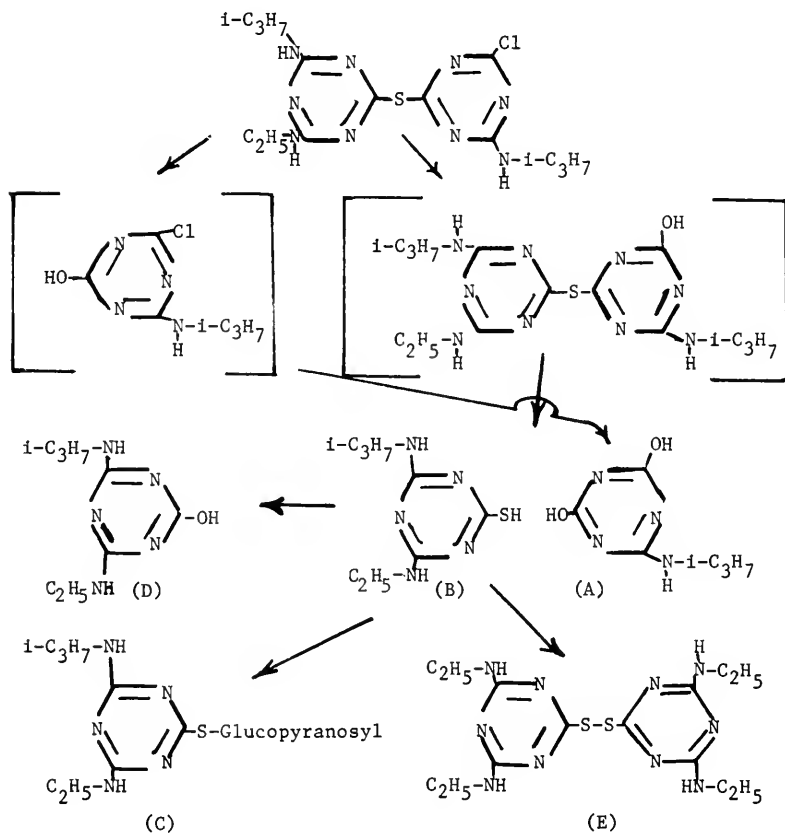
After oral ingestion by a rat, ^{14}C-Cyanazine (XLIII) was rapidly
metabolized. About 40% of the administered label was excreted
via urine and 47% via feces. The main route of metabolism of
Cyanazine in rats was via N-desethylation to give the amine compound
XLIX. In urine in addition to this compound, the N-acetylcysteinyl
derivatives XLVII and XLVIII were also found. Dechlorination
produced the 2-hydroxy compound (LIV). The cyano group hydrolyzed
to the amide (L) and then the carboxyl analog. In feces the major
metabolite was the 2-hydroxy compound LIV. Minor metabolites
detected were LVI, LI, XLIV and XLIX. Examination of bile revealed
the presence of the glutathione conjugates XLV and XLVI (Crayford
and Hutson, 1972; Hutson et al., 1970).

Spring and winter wheat and potatoes were grown under indoor conditions
in soils treated at planting with up to 1.5 Kg/ha of labeled herbicide.
The major degradation products were produced by hydrolysis to give the
amide and acid analogs of cyanazine. Hydrolysis of the chlorine also
occurred. In wheat the desethyl chloro acid formed. At time of harvest,
residues in all crops consisted primarily of the hydroxy acids. Whereas
in spring wheat and potatoes these acids were present in free and
conjugated forms, in winter wheat they were present almost entirely
as conjugates (Beynon et al., 1972c).

In soil, Cyanazine degradation proceeded initially by hydrolysis of
the nitrile group and then by slower and separate hydrolysis of the
2-chloro group. Some dealkylation of the cyanoisopropyl group to
give LVII also occurred. No hydroxy-cyanazine was observed. When
maize was grown in soils treated with Cyanazine, compound LII and
LVI were identified as the dealkylated analogs of the amide L and
the hydroxy-acid LIV. The dealkylated amide (LII) and acid (LV)
have been found as residues in the plant and in the soil used to
grow the maize. The hydroxy-acid (LIV) apparently was not
dealkylated in maize (Beynon et al., 1970, 1972b).

The half-life for Cyanazine in soils was 1.3 to 5 weeks (mean value
= 2.4 weeks). When applied to soil at 2 Kg/ha, Cyanazine residues
and metabolites declined rapidly. At 4 weeks, residues of Cyanazine
amide (L) and its desethyl analog (LII) were 0.5 ppm and 0.08 ppm,
respectively. Repeated annual applications did not cause a detectable
residue build up in soils (Beynon et al., 1972e).

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The hydrolysis of Cyanazine was studied over a temperature range of
25° to 75°C and over a range of pH from 1.5 to 12. In acid solution,
the only product identified after hydrolysis was 2-hydroxy-4-carboxy-
isopropylamino-6-ethylamino-s-triazine (LIV). The same hydroxy acid
was observed after alkaline hydrolysis but an intermediate was identi-
fied as 2-chloro-4-amidoisopropylamino-6-ethylamino-1,3,5-triazine (L).
Another compound was also identified as 2-chloro-4-amino-6-ethylamino-
1,3,5-triazine (LVII) (Brown et al., 1972).

GS-14254 [2-sec-Butylamino-4-ethylamino-6-methoxy-s-triazine]

Rats fed GS-14254 (XXVII), excreted 15 metabolites in the urine.
Over 90% of the excreted metabolites was accounted for by four
compounds: 2,4-diamino-6-methoxy-s-triazine (XXIX);. 2-amino-
4-(4-hydroxy-sec-butylamino)-6-methoxy-s-triazine (XXXVIII);
2,4-diamino-6-hydroxy-s-triazine (XXXIII); and 2-amino-4-hydroxy-
6-(4-hydroxy-sec-butylamino)-s-triazine (XXXIV). After feeding
compound XXXV to rats, two urinary metabolites were identified
as compounds XXXVI and XXXVII. When the latter two were fed to
rats, only the parent compounds were recovered (Larson et al.,
1970).

After oral administration of a single dose of GS-14254 (XXVII) to a
lactating cow, 89% of the ^{14}C was recovered within 120 hours. Seven
urinary components represented 77% of the urinary radioactivity. A
total of 19 components in cow urine was indicated by ion-exchange
chromatography. A treated goat gave a similar pattern or urinary
metabolites. Seven compounds (XXVIII - XXXIV) were identified. Three
compounds (XXIX, XXX and XXXI) were also observed in the feces (Bakke
et al., 1971).

PROMETRYNE   [2,4-Bis(isopropylamino)-6-methylthio-s-triazine]

Both cotton (Gossypium hirsutum L.) and soybean (Glycine max Merr.)
converted some prometryne (XXIV) to the hydroxy analog (XXV) (Sikka
and Davis, 1968).

When prometryne was irradiated at 253.7 nm. in methanol, ethanol,
n-butanol, benzene or water, 4,6-bis(isopropylamino)-s-triazine
(XXVI) was formed (Pape and Zabik, 1969 and 1970).

After incubation of ring-labeled prometryne with Hagerstown silty
clay loam for 15 months at 30°C, some of the radioactivity could
not be removed from a humic acid type fraction. The sulfoxide
and sulfone of prometryne were observed, as well as three unknown
compounds (Kearney and Plimmer, 1969).

<u>PROPAZINE</u>   [2,4-Bis(isopropylamino)-6-chloro-<u>s</u>-triazine]

Ultraviolet irradiation of propazine (XVIII) in water yielded the
hydroxypropazine (XIX).   In methanol and ethanol, the corresponding
methoxy and ethoxy analogs formed (Pape and Zabik, 1969 and 1970).

SIMAZINE [2,4-Bis(ethylamino)-6-chloro-s-triazine]

The non-enzymatic hydrolysis of simazine (XII) to hydroxysimazine (XIII)
was catalyzed by 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one. Results
of the studies indicated that hydrolysis may be catalyzed by molecular
aggregates of this compound (Tipton et al., 1971).

In corn, the primary product of hydroxysimazine metabolism was the de-
alkylated material 2-amino-4-ethylamino-6-hydroxy-s-triazine (XIV). A
second dealkylation gave rise to ammeline (XV) (2,4-diamino-6-hydroxy-s-
triazine). Some $^{14}CO_2$ was evolved in corn from ^{14}C-ring labeled simazine.
It was felt that this occurred after the sequence of dealkylation,
replacement of $-NH_2$ by $-OH$, and subsequent ring opening (Montgomery et al.,
1969). Simazine was also metabolized by wild cane (Sorghum bicolor L.).
Hydroxysimazine and two peptide conjugates (XVI and XVII) found were
similar to those of atrazine (Thompson,1972).

Green algae (Ankistrodesmus braunil and Chlorosarcina sp.) metabolized
simazine. No metabolites were identified (Kruglov and Paromenskaja, 1970).
UV irradiation of simazine in water formed hydroxysimazine. By a similar
mechanism, irradiation in methanol or ethanol yielded the methoxy and
ethoxy analogs (Pape and Zabik, 1969 and 1970).

Simazine, added to pots containing cymbidium pseudobulbs, was converted
to hydroxy simazine (XIII) and unidentified materials (Bivins et al.,
1968).

Simazine was readily absorbed and distributed in spruce seedlings.
Degradation of simazine took place in roots and stem to the hydroxy
analog XIII and two unidentified compounds. Metabolites, but no
simazine,were observed in needles. The glucose derivative of benz-
oxazinone was found in all parts of the seedlings and was probably
responsible for the hydrolysis of simazine (Lund-Hoie, 1969).

<u>SIMETRYNE</u> [2,4-Bis(ethylamino)-6-methylthio-<u>s</u>-triazine]

Ultraviolet irradiation (at 253.7 nm) of simetryne (XXII) in methanol, ethanol, <u>n</u>-butanol, benzene or water produced 4,6-bis(ethylamino)-<u>s</u>-triazine (XXIII) (Pape and Zabik, 1969 and 1970).

<u>WL 9385</u> [2-Azido-4-<u>tert</u>-butylamino-6-ethylamino-<u>s</u>-triazine]

When applied to wheat, WL 9385 (XXXV) was metabolized by reduction of
the azido group to an amine and by dealkylation. Compounds XL, XLI
and XLII were found. In treated soils, compounds XL and XLI were
identified (Beynon and Wright, 1969a).

<u>Trichlorphon</u> (Dipterex, Trichlorfon, Chlorofos, Neguvon, Tugon,
Dylox) [$\underline{O},\underline{O}$-Dimethyl 2,2,2-trichloro-1-hydroxy-
ethylphosphonate]

(See also DDVP)

[14]C-Methoxy-labeled trichlorphon was incubated with human serum
for 3 hours at 37.5°C. After separation of the metabolites, [14]C-
activity appeared in three amino acid fractions when the serum
protein was hydrolyzed and analyzed (Dedek and Lohs, 1970a).

[14]C-CH$_3$O-trichlorphon was administered i.v. or i.p. to rats. Most
of the label found in the liver was not extractable. The specific
activity of ^{14}C remained constant in the globulin and albumin
fractions after several ammonium sulfate precipitations, indicating
methylation of the protein (Dedek and Lohs, 1970b).

After intraperitoneal injections of ^{32}P-labeled trichlorfon into
rats, urine was collected and analyzed. The major detoxification
product was dimethyl phosphate. Some monomethyl phosphate, ortho-
phosphate, $\underline{O}$-demethyl dichlorvos, $\underline{O}$-demethyl trichlorfon, and two
unknowns were also observed. One of these was characterized as a
glucuronide containing trichlorfon but not further identified (Bull
and Ridgway, 1969).

In cotton leaves treated with trichlorfon, the major metabolites
were demethyl phosphate and an unknown. In addition to these com-
pounds, orthophosphate, monomethyl phosphate, dichlorvos, $\underline{O}$-demethyl
trichlorfon and $\underline{O}$-demethyl dichlorvos were also observed (Bull and
Ridgway, 1969).

Studies with insects revealed substantial differences between species
in the rate of diminution if external radioactivity and the accumula-
tion of internal radioactivity. After 4 hours, unabsorbed radio-
activity on green lacewing larvae was 72.5% of the dose, that on
tobacco budworms was 41% and 7% on lygus bugs. After 1 hour lygus
bugs accumulated 57.3% of the dose internally but the other two
species never exceed 8% (Bull and Ridgway, 1969).

In the digestive fluids of the silkworm <u>Bombyx</u> <u>mori</u>, DDVP formed
from trichlorphon under a wide range of pH (Sugiyama and Shigematsu,
1969).

Compounds Observed					
	Lygus Bug		Tobacco budworm		Green Lacewing	
	External	Internal	External	Internal	External	Internal
H_3PO_4 + $CH_3OPO_3H_2$	+	+	+	+	+	−
$(CH_3O)_2PO_2H$	+	+	+	+	+	+
Trichlorfon	+	+	+	+	+	+
Dichlorvos	+	+	−	+	−	+
O-demethyl trichlorfon	+	+	−	−	−	−
Unknown A	+	+	+	+	+	+
Unknown C	+	+	−	−	−	−

Half-life at 37.5 degrees C

System	Trichlorphon
Buffer, pH 7.0	7.3 hr
Buffer, pH 8.0	1.4
Cow blood, pH 7.7 (in vitro)	0.8

(Kuhnert et al., 1963).

TRIFLURALIN [α,α,α-Trifluoro-2,6-dinitro-N,N-di-n-propyl-p-toluidine]

Labeled trifluralin was incubated in artificial rumen fluid.
Over 98% of the label was recovered in extracts and spent fluid,
an indication that trifluralin was not degraded to radioactive
gases. Degradation was rapid initially to compound VII which was
then converted to compound VIII. After 11 hours, trifluralin was
not detectable. Compound III and trace amounts of II were also
observed. A compound believed to be α,α,α-trifluoro-N_4-propyl-
toluene-3,4,5-triamine(V) was also observed (Golab èt ál., 1969).

The fate of labeled trifluralin in a lactating cow was studied
and found to be similar to that in the artificial bovine rumen
fluid. In feces, in addition to unreacted trifluralin, compounds VII
and VIII and traces of II and IX were found. When a goat was
administered labeled trifluralin, radioactivity was found in urine
and feces. The principal metabolite in both urine and feces extracts
was compound VIII. In the feces extract, the only other metabolite
found was the triamine(VI). The urine extract contained traces of
compounds III, IV, VII and possibly V (Golab et al., 1969).

Trifluralin was incubated with rumen microorganisms. Of 12
characterized rumen bacterial strains, 10 did not degrade trifluralin.
Bacteroides ruminicola subsp. brevis and Lachnospira multiparus
degraded trifluralin to compounds VIII, III, VII, V, II (Williams
and Feil, 1971).

In crude extracts of peanuts (Arachis hypogaea L.), initial degradation
removed one of the propyl groups. Compounds III, IV, VII, and VIII
were also observed. Two other compounds were seen but not completely
characterized: one contained the CF_3, at least one NO_2, OH in place of
the N,N-dipropyl; the other compound contained a carboxyl in place
of the CF_3 and at least one nitro group. Similar results were obtained
when extracts of sweet potato (Ipomoea batatas L) were used (Biswas
and Hamilton, 1969).

(VII)   (I)   (IX)

(VIII)   (III)   (II)

(IV)   (VI)   (V)

373
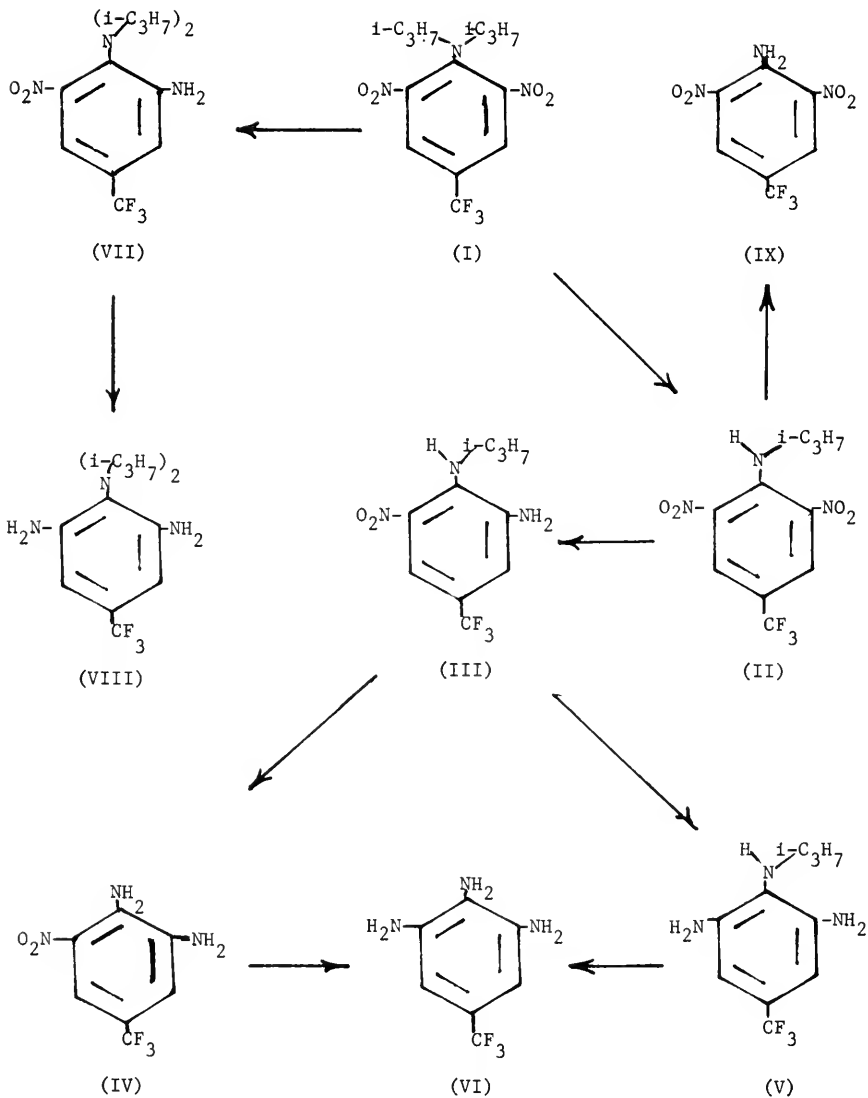
Ring-labeled triphenyl-lead acetate was administered orally in
dimethyl sulfoxide to rats at a dose level of 25 mg/kg. Urine,
feces and expired air were collected daily for seven days.
Analyses indicated that during this period, 25% of the label
was found in urine, 29% in feces and 20% in expired air. At
a dose level of 200 mg/kg, no lead was found in urine but 75%
was found in feces in 7 days. Expired ^{14}C was almost entirely
benzene with little $^{14}CO_2$ (1%). The ^{14}C of the urine was present
mainly as phenyl sulfate. A small amount of quinol sulfate was
also present (Williams et al., 1971).

<u>UC-22463</u> (Rowmate) [3,4-Dichlorobenzyl <u>N</u>-Methylcarbamate]

Male rats were fed labeled UC-22463 for seven days. 31% of the
N-methyl label was excreted in urine and 45% as CO_2. About 95%
of benzyl label was excreted in urine but none as CO_2. Fecal
excretion amounted to 3 to 5% of the dose. Urinary metabolites
were identified as 3,4-dichlorobenzyl glucuronide (5%), 3,4-
dichlorohippuric acid (63%) and 3,4-dichlorobenzoic acid (6%).
A metabolite identified as 3,4-dichlorobenzoyl glucuronide (5%)
was also found in urine (Knaak and Sullivan, 1968).

Labeled herbicide was applied to plants. The parent compound
and metabolites were isolated and identified by mass spectral
analyses and cochromatography with standards. Metabolic products
identified were: 3,4-dichlorobenzyl alcohol; 3,4-dichloro-2-
hydroxybenzyl alcohol; 3,4-dichlorobenzoic acid; 3,4-dichlorobenzyl
carbamate; and 3,4-dichlorobenzyl hydroxymethylcarbamate (Andrawes
and Herrett, 1969).
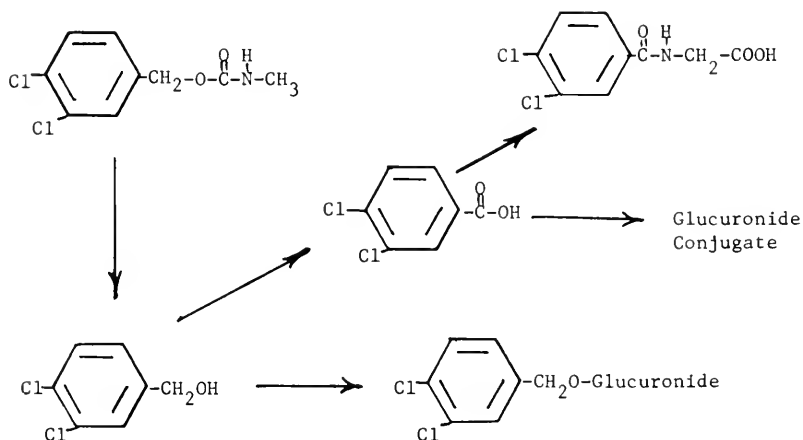
UC-34096 underwent spontaneous decomposition to 4-hydroxy-N-formyl-o-toluidine. When left standing for 40 days at room temperature, an aqueous solution yielded four compounds believed to be UC-34096(I), 4-(methylcarbamoyloxy)-o-toluidine(III), 4-(methylcarbamoyloxy)-N-formyl-o-toluidine(II), and 4-hydroxy-N-formyl-o-toluidine(IV) (Locke et al., 1971).
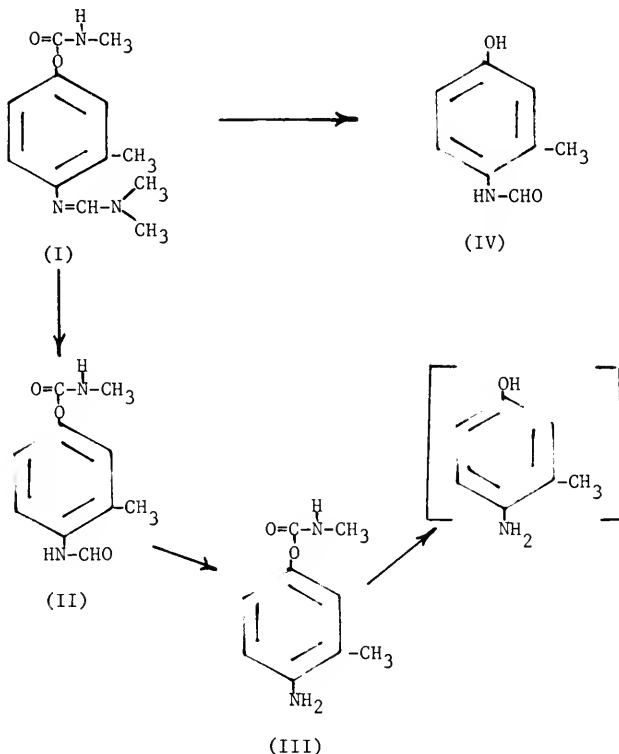
<u>UK-3833</u> [2-Isopropylaminomethyl-6-methyl-7-nitro-1,2,3,4-
              tetrahydroquinoline]

The metabolism of UK-3833 was investigated in mouse, rat, rabbit,
and rhesus monkey. In the urines, four metabolites were found. The
6-hydroxymethyl (II), 6-carboxy (III), 2-carboxy (IV), and 2-carboxy-
6-hydroxymethyl (V) analogs were identified. Compounds IV and V were
not found in the rat (Kaye and Woolhouse, 1972).
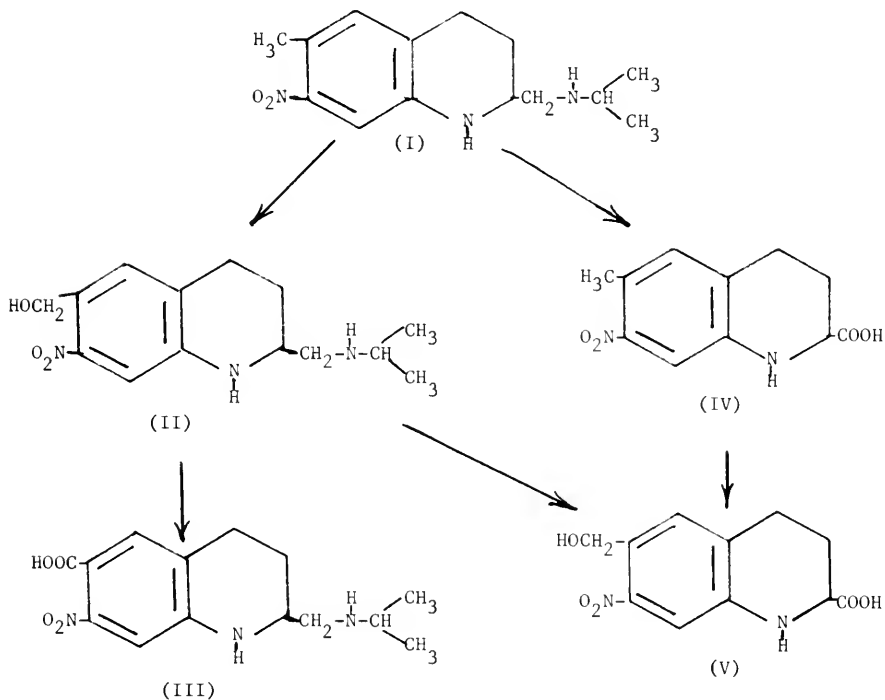
UREAS

(See also Anilines)

Chlorbromuron [3-(3-Chloro-4-bromophenyl)-1-methoxy-1-methylurea]

Diuron   [3-(3,4-Dichlorophenyl)-1,1-dimethylurea]

Fluometuron   [1,1-Dimethyl-3-(α,α,α-trifluoro-m-tolyl)urea]

Linuron   [3-(3,4-Dichlorophenyl)-1-methoxy-1-methylurea]

Metobromuron [3-(p-Bromophenyl)-1-methoxy-1-methylurea]

Metoxuron   [3-(3-Chloro-4-methoxyphenyl)-1,1-dimethylurea]

Monuron   [3-(p-Chlorophenyl)-1,1-dimethylurea]

Siduron   [1-(2-Methylcyclohexyl)-3-phenylurea]

CHLORBROMURON [3-(3-Chloro-4-bromophenyl)-1-methoxy-1-methylurea]

After exposure of corn seedlings to chlorbromuron, the plants were analyzed. In addition to unchanged herbicide, corn tops and roots contained the demethyl and de-methoxy analogs, the completely de-alkylated compound, 3-chloro-4-bromoaniline and chlorbromuron conjugate. The same metabolites were found in cucumber shoots and roots (Nashed et al., 1970b).

The soil fungus Rhizoctonia solani degraded chlorbromuron to the demethyl analog. Other metabolites were observed but not identified. When R. solani was incubated with the demethylated metabolite, a compound with R_f equal to 3-(3-chloro-4-bromophenyl)urea was observed (Weinberger and Bollag, 1972).

DIURON   [3-(3,4-Dichlorophenyl)-1,1-dimethylurea]

After ingestion of diuron, a woman excreted via urine the de-methyl and completely de-alkylated analogs. Some 3,4-dichloroaniline was probably also excreted (Geldmacher-v. Mallinckrodt and Schussler, 1971).

Studies with the soil organism Bacillus sphaericus indicated this organism to be incapable of metabolizing diuron (Wallnofer, 1969). The incubation of 500 ppm diuron with soil yielded about 1 ppm DCA and no detectable TCAB. Even at high DCA concentrations, little TCAB was observed. It was believed, therefore, that DCA was not the prime precursor for TCAB formed in soil (Belasco and Pease, 1969).

FLUOMETURON [1,1-Dimethyl-3-(α,α,α-trifluoro-m-tolyl)urea]

The pathway of degradation of fluometuron in a sandy loam soil involved a two step de-alkylation, probably followed by hydrolysis to form the aniline derivative. When the trifluoromethyl group was labeled, some $^{14}CO_2$ was observed. The mono- and di-demethyl compounds, as well as the aniline product, were observed (Bozarth and Funderburk, 1971).

Bacillus spaericus was unable to metabolize fluometuron (Wallnofer, 1969; Wallnofer and Bader, 1970; Engelhardt et al., 1971).

<u>LINURON</u> [3-(3,4-Dichlorophenyl)-1-methoxy-1-methylurea]

In greenhouse studies, linuron entered the corn (<u>Zea</u> <u>Mays</u> L.), soybean (<u>Glycine</u> <u>max</u> L.) and crabgrass (<u>Digitaria</u> <u>sanguinalis</u> L.) with the absorbed water. The demethyl linuron and 3,4-dichloroaniline were found in the tissues. The studies indicated that some linuron was bound within the plant (Nashed and Ilnicki, 1970).

When labeled linuron was incubated with <u>Bacillus</u> <u>sphaericus</u>, $^{14}CO_2$ was released and 3,4-dichloroaniline was found in the media (Wallnofer, 1969; Wallnofer and Bader, 1970). In other studies, a linuron-inducible enzyme was obtained from <u>Bacillus</u> <u>sphaericus</u>. This acylamidase degraded linuron by hydrolysis of the amide bond with subsequent release of CO_2 and <u>N</u>,<u>O</u>-dimethyl hydroxylamine. This enzyme was specific for methoxy-substituted phenylureas and did not hydrolyze 1,1-dimethyl phenylureas (Engelhardt et al., 1971 and 1972).

After exposure to sunlight for several months, linuron yielded 3,4-dichlorophenylurea, de-methoxy linuron and 3-(3-chloro-4-hydroxy phenyl)-1-methoxy-1-methylurea (Rosen et al., 1969).

N,O-dimethyl
hydroxylamine
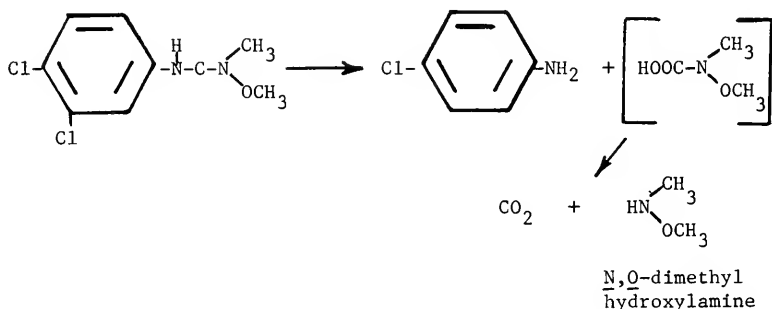
<u>METOBROMURON</u>   [3-(<u>p</u>-Bromophenyl)-1-methoxy-1-methylurea]

Cultures of the soil organisms <u>Talaromyces wortmanii</u>, <u>Fusarium</u>
<u>oxysporum</u>, <u>chlorella vulgaris</u> and a <u>Bacillus</u> sp. were incubated
with metobromuron.   <u>Talaromyces wortmanii</u> and <u>Fusarium oxysporum</u>
acetylated p-bromoaniline.   In other studies, demethyl and de-
methoxy metobromuron, <u>p</u>-bromophenylurea and the <u>p</u>-bromoacetanilide
were also found (Tweedy et al., 1970a & b).   An acylamidase found
in <u>Bacillus sphaericus</u> was capable of splitting the amide bond of
metobromuron (Engelhardt et al., 1971 ; Wallnofer, 1969; Wallnofer
and Bader, 1970).

METOXURON [3-(3-Chloro-4-methoxyphenyl)-1,1-dimethylurea]

Soil/water slurries containing compound II turned pink after about
8 days and remained so for several months. After removal of the
soil and CHCl₃- extraction of the aqueous phase, a pink product
and a colorless compound were obtained. These were identified by
TLC, mass spectra, n.m.r. and synthesis as: N-(3-chloro-4-methoxy-
phenyl)-2-chloro-1,4-benzoquinone monoimide (III) and 2,3'-dichloro-
4-hydroxy-4'-methoxydiphenylamine (IV). TLC of acetone extracts
of soil indicated several additional compounds. One was identified
as 3,3'-dichloro-4,4'-dimethoxyazobenzene (V). The other compound,
red and probably a dimer, was not further characterized (Briggs and
Ogilvie, 1971). Coupling products were not observed in soil or
slurries that contained 25 ppm metoxuron.

The diagram below depicts reactions of the aniline compound that
could arise from cleavage of metoxuron.
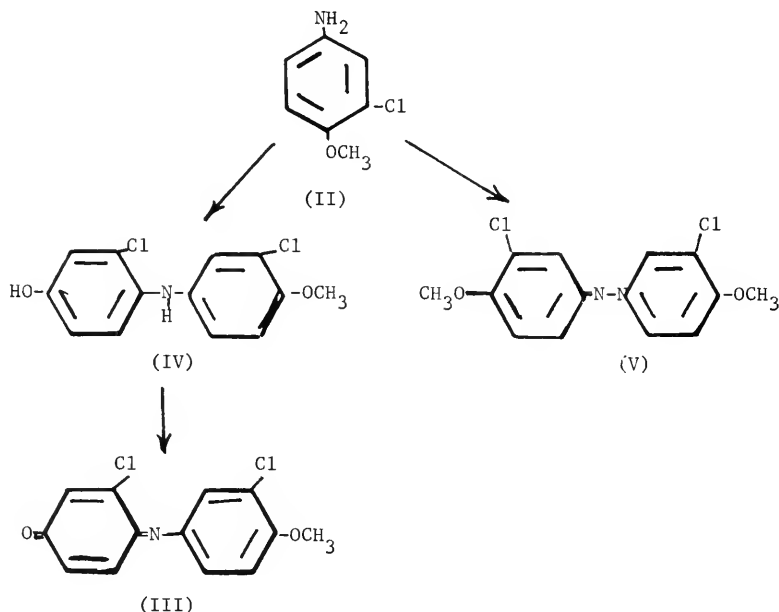
MONURON [3-(p-Chlorophenyl)-1,1-dimethylurea]

Cotton plants degraded monuron to monomethylmonuron and p-chloro-
phenylurea by successive demethylations and then to p-chloroaniline
by hydrolysis of the amide bond. In the presence of moderate amounts
of carbaryl, degradation beyond the mono-demethylation was inhibited.
Furadan was not inhibitory but 4-benzothiophene-N-methylcarbamate
was as effective as carbaryl (Swanson and Swanson, 1968).

A cotton leaf microsomal oxidase system was isolated and partially
characterized. Monuron was demethylated in the presence of NADPH
or NADH and oxygen. An intermediate in the oxidation of the mono-
demethylated monuron has been tentatively identified as 3-(4-chloro-
phenyl)-1-hydroxymethylurea. One mole of formaldehyde also arises
for each mole of herbicide. This enzyme system was also found in
plantain, buckwheat, wild buckwheat, and broadbean. The hydroxy-
methyl analog rapidly decomposed to 4-chlorophenylurea and
formaldehyde (Frear et al., 1969 and 1970; Tanaka et al., 1972a and
b).

In other studies, excised cotton leaves metabolized monuron to the
unstable N-hydroxymethyl analog which was then conjugated to form
the glucoside. N-Demethylation then yielded monomethylmonuron and
formaldehyde. Further metabolism produced 3-(4-chlorophenyl)-1-
hydroxymethylurea. This metabolite was also conjugated as the
glucoside (Frear and Swanson, 1971 and 1972).

Exposure of monuron to sunlight gave rise to: 3-(p-chlorophenyl)-1-
formyl-1-methylurea, 1-(p-chlorophenyl-3-methylurea, 4,4'-dichloro-
carbanilide, 3-(4-chloro-2-hydroxyphenyl)-1,1-dimethylurea, 1-(p-
chlorophenyl)-3-formylurea, 4'-chloroformanilide, p-chlorophenylurea
and p-chloroaniline (Crosby and Tang, 1969).

In methanol and under anaerbic conditions, photolysis of monuron
produced fenuron and a minor amount of methyl p-chlorophenyl-
carbamate. Photolysis of fenuron produced aniline, N,N-dimethyl-
2-aminobenzamide and N,N-dimethyl-4-aminobenzamide (Mazzacchi and
Rao, 1972).

<u>SIDURON</u> [1-(2-methylcyclohexyl)-3-phenylurea]

When fed to a dog, siduron gave rise to three metabolites found in the urine. These metabolites were present as conjugates of 1-(4-hydroxyphenyl)-3-(2-methylclohexyl)urea, 1-(4-hydroxy-2-methylcyclohexyl)-3-phenylurea and 1-(4-hydroxy-2-methylcyclo-hexyl)-3-(4-hydroxyphenyl)urea (Belasco and Reiser, 1969). The same metabolites, but not conjugated, were found in soil (Belasco and Langsdorf, 1969).

URACILS

BROMACIL [5-Bromo-3-sec-butyl-6-methyluracil]

Male rats were maintained for one month on a diet containing
1250 ppm of bromacil(I). Urine was collected during the 3rd and
4th week and analyzed. Seven metabolites were isolated: 5-bromo-3-
sec-butyl-6-hydroxymethyluracil(II); 5-bromo-3-(2-hydroxy-1-methyl-
propyl)-6-methyluracil(III); 5-bromo-3-(2-hydroxy-1-methylpropyl)-6-
hydroxymethyluracil(IV); 3-sec-butyl-6-hydroxymethyluracil(V); 5-bromo-
3-(3-hydroxy-1-methylpropyl)-6-methyluracil(VI); 3-sec-Butyl-6-
methyluracil(VII); and an unidentified bromine-containing compound(VIII)
of molecular weight 339 (Gardiner et al., 1969).

When herbicide concentrations in the feed of cows was 5 and 30 ppm,
secretion of the intact compound in the milk reached concentrations
of 0.019 and 0.13 ppm, respectively. Bromacil was absent in urine
and feces samples. In the presence of rumen fluid, decomposition
of bromacil did not occur for seven hours. The compound was stable
when incubated with the 10,000-G supernatant homogenized liver
fraction for one hour (Gutenmann and Lisk, 1970).

In laboratory studies, 25 to 32% of herbicide applied to soil was
lost as CO_2 in six to nine weeks. Soil residues contained six
metabolites: Compounds I, II, III, IV, VI and an unidentified
material. The half-life in soil was about 5-6 months (Gardiner et al.,
1969).

In other studies, orange plants were maintained for 4 weeks in
sand on a nutrient solution containing 10 ppm bromacil-2-^{14}C. Less
than 5% of the activity was taken up. In addition to bromacil,
compound II and an unidentified metabolite were found (Gardiner
et al., 1969).

(VII)   (V)

(I)

(II)   (VI)

(IV)   (III)

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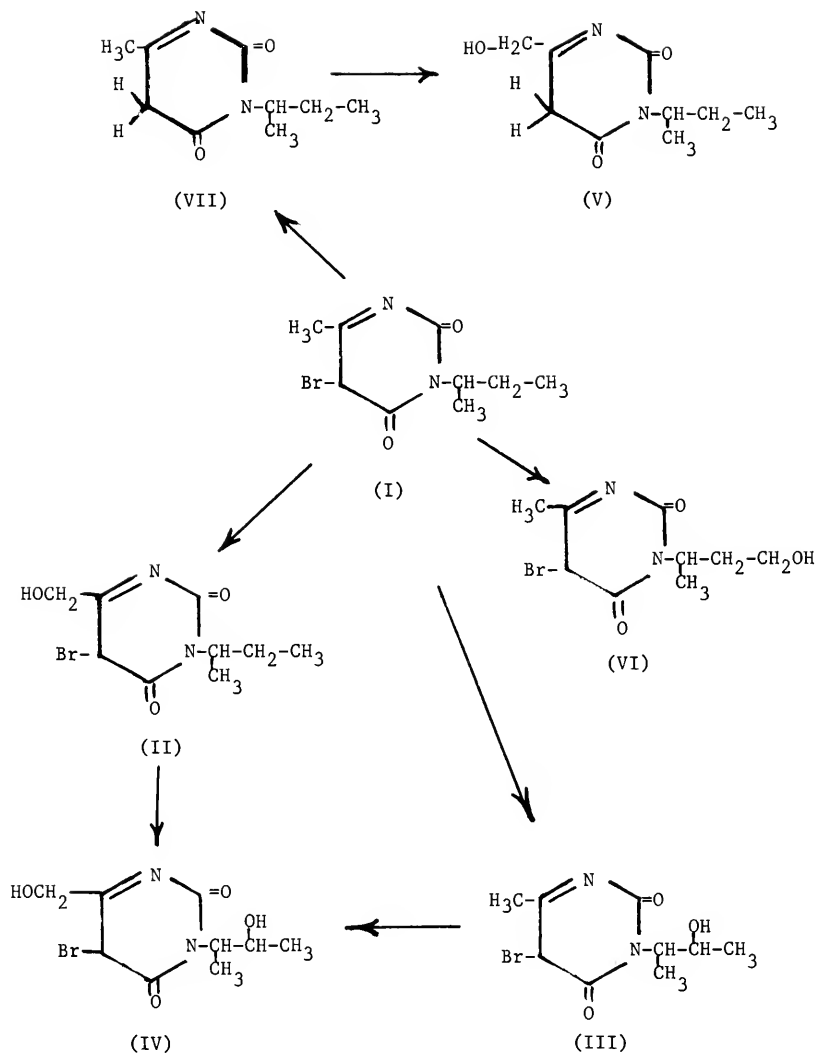
TERBACIL [3-tert-Butyl-5-chloro-6-methyluracil]

Female beagle dogs were fed diets containing terbacil(I). Analysis of collected urine indicated that the main metabolite was 3-tert-butyl-5-chloro-6-hydroxymethyluracil(II). In addition to this, several other metabolites were also observed: 6-chloro-2,3-dihydro-7-(hydroxymethyl)-3,3-dimethyl-5H-oxazolo-(3,2-a)pyrimidin-5-one(III); 6-chloro-2,3-dihydro-3,3,7-trimethyl-5H-oxazolo(3,2-a)pyrimidin-5-one(IV); 3-tert-butyl-6-hydroxymethyluracil(V); 3-tert-butyl-6-formyluracil(VI); and an unknown chlorine-containing compound of molecular weight 293 (Gutenmann and Lisk, 1969).

In laboratory studies, about 25-32% of applied carbon-14 was lost as CO_2. The half life was about 5-6 months (Gardiner et al., 1969).

| | Rate of Degradation in reciprocal months | | Arrhenius activation energy kcals/mole |
	13.2°C	31.2°C	
Bromacil	0.14	0.19	3.0
Terbacil	0.37	0.59	6.1

(Zimdahl et al., 1970)

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H₃C... structures with labels (IV), (I), (II), (III), (V), (VI)

(IV)

(I)

(II)

(III)

(V)

(VI)

390
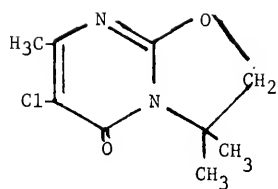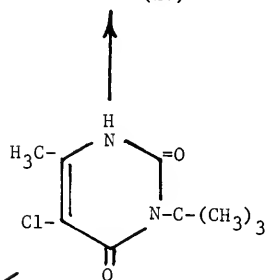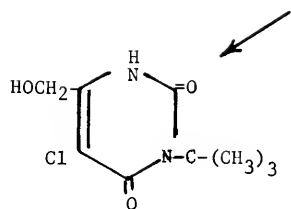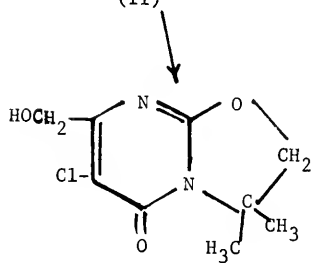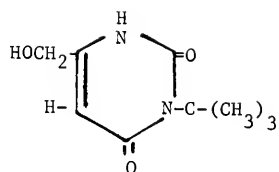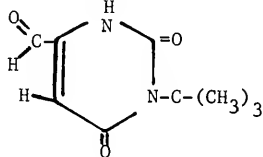
<u>VCS-438</u> [2-(3,4-dichlorophenyl)-4-methyl-1,2,4-oxadiazolidine-
3,5-dione]

When VCS-438 was fed to a lactating cow, no residues were detected
in milk, urine, or feces. The compound was also stable when incu-
bated with 10,000G supernatant of beef liver. When incubated with
rumen fluid, VCS-438 decomposed with formation of 1-(3,4-dichloro-
phenyl)-3-methylurea (Gutenmann et al., 1972).
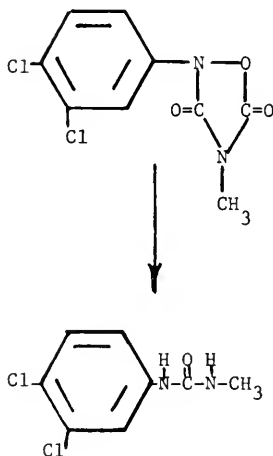
<u>Warfarin</u> (Coumafene, Zoocoumarin, WARF 42)   [3-(α-Acetonylbenzyl)-
4-hydroxycoumarin]

After oral administration of warfarin to humans, several metabolites
were observed in the urine and plasma. In addition to 7-hydroxy
warfarin, the 6-hydroxy analog and the diastereoisomeric warfarin
alcohols were observed (Lewis and Trager, 1971).

Rats, given i.p. injections of labeled warfarin, excreted 90% of
the radioactivity in urine (60%) and feces (30%) within two weeks
after administration. The remaining radioactivity was excreted
over a 90 day period. No $^{14}CO_2$ was detected. Chromatography in-
dicated that the same six metabolites were in urine and feces but
were different quantitatively. These were resolved and identified
as 6-hydroxy-, 7-hydroxy-, 8-hydroxy-, and 4^1-hydroxy-warfarin and
2,3-dihydro-2-methyl-4-phenyl-5-oxo-γ-pyrano (3,2-c) (1) benzopyran.
The glucuronide of 7-hydroxy warfarin was also found (Barker et
al., 1970). Comparison of drug-metabolizing enzyme systems of
warfarin susceptible and resistant male rats indicated higher con-
centrations of the enzymes in resistant rats but no differences
in the rate of formation of the metabolites (Davis & Davies, 1970;
Taylor and Townsend, 1970) or in their relative proportions (Hermodson
et al., 1969).

Plasma half-life of (-) warfarin in male rats was found to be
15.4 $\pm$ 2.8 hrs; and that of (+) warfarin, 8.6 $\pm$ 1.6 hours (Breckenridge
and Orme, 1972). Similar results were observed in other studies.

	Sex	Enantiomer	$t_{1/2}$ (h)
Resistant rats	♂	+	7.3
(SH)		−	12
	♀	+	9
		−	23
Non-resistant	♂	+	7.6
(Sprague-Dawley)		−	11
	♀	+	11.6
		−	33

(Henwick, 1972)

Warfarin Alcohol
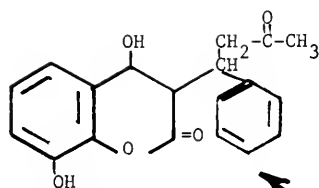
4'-Hydroxywarfarin
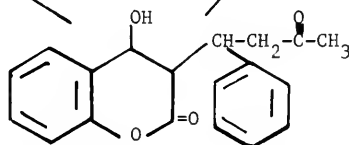
8-Hydroxywarfarin

Warfarin
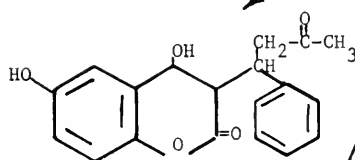
6-Hydroxywarfarin
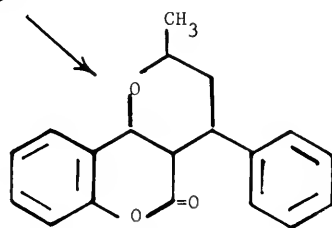
-γ-pyrano(3,2-c)(1) benzopyran
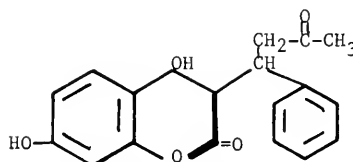
7-Hydroxywarfarin → Glucuronide

The amount of zectran recovered after incubation with human liver
did not differ greatly from that recovered after incubation with
rat liver. Four compounds made up the majority of metabolites pro-
duced: 4-methylformamido-3,5-xylyl methylcarbamate, 4-amino-3,5-
xylyl-methylcarbamate, 4-methylamino-3,5-xylyl-methylcarbamate, and
4-dimethylamino-3,5-xylyl-N-hydroxymethylcarbamate. Some 4-dimethyl-
amino-3,5-xylenol was also present. Less than 2% of the ^{14}C-carbonyl
appeared as $^{14}CO_2$ (Strother 1970 and 1972). Similar results were
obtained with preparations from kidney and blood of dogs (Wheeler
and Strother, 1971).

N-Acetylation of zectran eliminated its toxicity in mice but did not
alter its toxic effects on spruce budworm. Mice hydrolyzed acetyl
zectran and produced CO_2, the phenol, and an unidentified water-
soluble compound. Spruce budworm removed the acetyl group. The
re-generated zectran was metabolized in part to 4-methylamino-3,5-
xylyl-N-methylcarbamate (Miskus et al., 1969).

ZINC PHOSPHIDE [Zn_3P_2]

In aqueous suspension and in the presence of fat or oil, particles
of zinc phosphide are preferentially adsorbed to the surface of
the fat or oil and can float. When doses in excess of the LD_{50}
were ingested, death was rapid and phosphine was detectable in
the liver. At lower doses, when animals were sacrificed more
than 24 hours after ingestion, no phosphine was detectable in
the liver. However, addition of acid to the tissue produced a
faint brown coloration when the evolved gases were passed through
a filter paper wetted with methanolic silver nitrate. The main
urinary product in rats and guinea pigs was hypophosphite (Curry
et al., 1959).

The interaction of phosphine with plant and mineral substances
was studied with phosphine- ^{32}P. In the environment, phosphine
not immediately dissipated in the air would probably form heat-
stable non-volatile phosphorus compounds, water soluble oxy-acids;
and in moist soil and in the presence of inorganic materials,
insoluble non-volatile compounds were formed (Hilton and Mee, 1972).

In wheat and flour, phosphorous residues are largely water-soluble
and consisted mainly of hypophosphite and phosphite. Phosphine
reduced cystine and formed cysteine and phosphorus oxy-acids.
In extracts of insects poisoned with PH_3, the phosphorus was pre-
dominantly in the lower oxy-acid state (Robinson and Bond, 1970).

ZINOPHOS (Thionazin) [<u>O</u>,<u>O</u>-Diethyl-<u>O</u>-2-pyrazinyl phosphorothioate]

Soil was treated with zinophos shortly after planting. Residues
were determined on soil extracts from samples taken at intervals
up to 12 weeks after application. Analyses demonstrated that the
rate of disappearance of zinophos varied considerably on different
agricultural soil types. Detectable amounts remained for one year
in Church Field soil (pH 5.4) but in High Field (pH 7.3) no
residues were detected after this period. Zinophos half-life
in soils varied from about 5-12 days at low dosage (5ppm) to
about 9-22 days at high dosage (20 ppm) (Pain and Skrentny, 1969).

ZYTRON [O-(2,4-Dichlorophenyl)-O-methyl-N-isopropylphosphoramidothioate]

Zytron was administered in feed to a cow. Nearly all of the
herbicide was converted to 2,4-dichlorophenol and excreted via urine.
Similarly, when zytron was incubated with the 10,000 G max super-
natant fraction of beef liver, 2,4-dichlorophenol was formed.
No residues of the phenol or zytron were observed in milk or
feces. The actual form of the urine metabolite was not determined
but may have been in the form of a glucuronide (St. John, Jr.,
and Lisk, 1970).

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Dimethoate analogs	Boiling point		Relative rate of hydrolysis by sheep liver amidase
	$^{\circ}C$	mm Hg	
1. $(CH_3O)_2$-$\overset{S}{\overset{\|}{P}}$-S-$CH_2$-$\overset{O}{\overset{\|}{C}}$-NH-$CH_3$			100 %
2. $\quad$ -NH-C_2H_5			86
3. $\quad$ -NH-C_3H_7(n)			134
4. $\quad$ -NH-C_4H_9(n)			39
5. $(C_2H_5O)_2$-$\overset{S}{\overset{\|}{P}}$-S-$CH_2$-$\overset{O}{\overset{\|}{C}}$-$NH_2$	(m.p.57-58)		
6. $(C_2H_5O)_2$-$\overset{S}{\overset{\|}{P}}$-S-$CH_2$-$\overset{O}{\overset{\|}{C}}$-NH-$CH_3$	130	0.1	66
7. $\quad$ -NH-C_2H_5	130	0.1	38
8. $\quad$ -NH-C_3H_7(n)	135	0.1	40
9. $\quad$ -NH-C_3H_7(i)			
10. $\quad$ -NH-C_4H_9(n)	135	0.05	27
11. $\quad$ -N-$(CH_3)_2$	120	0.05	168
12. $\quad$ -N-$(C_2H_5)_2$	130	0.15	0
13. $\quad$ -N-$(C_3H_7-n)_2$	130	0.10	
14. $\quad$ -N-$(C_3H_7-i)_2$	150	0.05	
15. $\quad$ -N-$(C_4H_9-n)_2$	130	0.15	
16. $(n-C_3H_7O)_2$-$\overset{S}{\overset{\|}{P}}$-S-$CH_2$-$\overset{O}{\overset{\|}{C}}$-NH-$CH_3$	120	0.05	0
17. $(i-C_3H_7O)_2$-	130	0.05	0
18. $(n-C_4H_9O)_2$-	140	0.05	
19. $(C_2H_5O)_2$-$\overset{S}{\overset{\|}{P}}$-S-$CH_2$-$CH_2$-$\overset{O}{\overset{\|}{C}}$-$NHCH_3$			0
20. $(C_2H_5O)_2$-$\overset{S}{\overset{\|}{P}}$-S-$\underset{CH_2}{CH}$-$\overset{O}{\overset{\|}{C}}$-$NHCH_3$	(m.p.62-63)		0

(Chen and Dauterman, 1971).

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Hydrolysis of organophosphates in distilled water

Compound	Percent Degradation					
	1 day	2 days	1 wk.	2 wks.	4 wks.	6 wks.
Malathion	6.5	19.1	40.7	69.3	91	--
Phosdrin	90	95.4	94.6	95.4	97.2	--
Methyl parathion	8.8	14.5	32	56.5	--	--
Ethyl parathion	4.0	6.7	18.2	32.7	68.8	82.2
Diazinon	4.8	9.5	37.4	53.7	91.7	--
Ronnel	11.6	39.6	95.1	--	--	--
Ethion	15.8	28.7	61.1	62.1	86.6	94.8

(Cowart et al., 1971)

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